Anodic Amide Oxidations: Total Syntheses of (−)-A58365A and (±)-A58365B[1]

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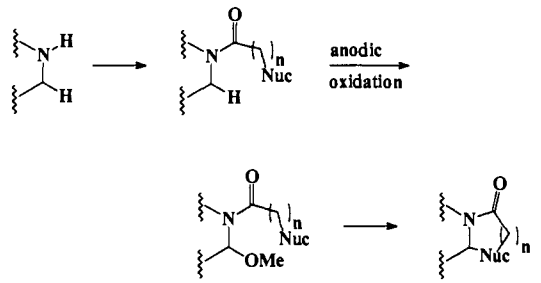
Abstract: An anodic amide oxidation–iminium ion cyclization strategy for annulating rings onto amines and amino acid derivatives has been used to synthesize the angiotensin-converting enzyme inhibitors (−)-A58365A and (±)-A58365B. Both syntheses take advantage of the ability of electrochemistry to selectively oxidize an amide in the presence of a disubstituted acetylene nucleophile. In the synthesis of A58365A, an electrolysis substrate (**10**) derived from proline was oxidized using constant current electrolysis conditions, an undivided cell, a carbon anode, and a 0.03 M tetraethylammonium tosylate in methanol electrolyte solution. An 83% isolated yield of the *N*-α-methoxyalkyl amide product **11** was obtained. The annulation procedure and formation of the desired 1-aza-2,5-dioxobicyclo[4.3.0]nonane ring skeleton were completed by treatment of the methoxylated amide with titanium tetrachloride followed by ozonolysis of the resulting vinyl chloride product. Keto amide **14** was obtained from this sequence in an 83% yield (69% over the three steps starting from the electrolysis precursor). In the synthesis of A58365B, a nearly identical procedure was used to convert an electrolysis substrate (**25**) derived from pipecolic acid into the required 1-aza-2,5-dioxobicyclo-[4.4.0]decane ring skeleton. In this case, the overall yield of the three-step procedure was 74%. The success of these two annulation procedures serves to highlight the utility of anodic amide-oxidation-based annulation procedures for constructing bicyclic lactam enzyme inhibitors.

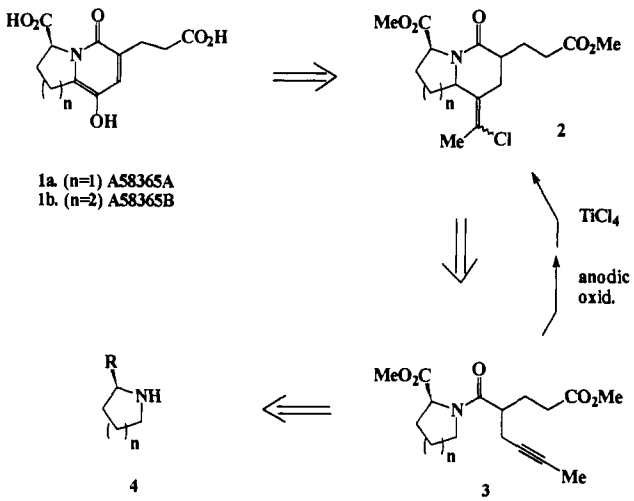
Introduction

Anodic amide oxidation–iminium ion cyclization strategies have the potential to serve as powerful tools for effecting the net annulation of lactam rings onto amines and amino acid derivatives.[2,3] An annulation procedure of this type would appear to



provide a method for constructing the bicyclic lactam rings often used to add conformational constraints to peptide mimetics.[4] The utility of this approach for constructing peptide analogs is based on the ability of electrochemistry to selectively functionalize amino acid derivatives.[5] But how general is this reaction, and can an anodic amide-oxidation-based procedure really be used to *simplify* the syntheses of a variety of lactam-based peptide mimetics and enzyme inhibitors?

Scheme I



• Abstract published in *Advance ACS Abstracts*, October 15, 1993.

(1) Taken in part from: Wong, P. L. Ph.D. Thesis, Washington University, St. Louis, MO, 1993.

(2) For pioneering work with anodic amide oxidations, see: (a) Ross, S. D.; Finkelstein, M.; Peterson, C. *J. Am. Chem. Soc.* **1964**, *86*, 4139. (b) Ross, S. D.; Finkelstein, M.; Peterson, C. *J. Org. Chem.* **1966**, *31*, 128. (c) Ross, S. D.; Finkelstein, M.; Peterson, C. *J. Am. Chem. Soc.* **1966**, *88*, 4657. For reviews, see: (d) Shono, T. *Tetrahedron* **1984**, *40*, 811. (e) Shono, T.; Matsumura, Y.; Tsubata, K. In *Organic Synthesis*; Saucy, G., Ed.; John Wiley and Sons, Inc.: New York, 1984; Vol. 63, p 206 and references therein. (f) Shono, T. In *Topics in Current Chemistry*; Steckhan, E., Ed.; Springer-Verlag: Berlin, Heidelberg, New York, 1988; Vol. 148, p 131.

(3) For examples of anodic amide-oxidation-based annulation procedures, see: (a) Ban, Y.; Okita, M.; Wakamatsu, T.; Mori, M. *Heterocycles* **1980**, *14*, 1089. (b) Ban, Y.; Irie, K. *Heterocycles* **1981**, *15*, 201. (c) Ban, Y.; Irie, K. *Heterocycles* **1982**, *18*, 255. (d) Ban, Y.; Okita, M.; Wakamatsu, T. *Heterocycles* **1983**, *20*, 401. (e) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300. (f) Shono, T.; Matsumura, Y.; Uchida, K.; Tagami, K. *Chem. Lett.* **1987**, 919. (g) Mori, M.; Kagechika, K.; Tohjima, K.; Shibasaki, M. *Tetrahedron Lett.* **1988**, *29*, 1409. (h) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. (i) Moeller, K. D.; Tarazi, S.; Marzabadi, M. R. *Tetrahedron Lett.* **1989**, *30*, 1213. (j) Moeller, K. D.; Wang, P. W.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. *J. Org. Chem.* **1991**, *56*, 1058. (k) Moeller, K. D.; Rothfus, S. L.; Wong, P. L. *Tetrahedron* **1991**, *47*, 583.

(4) For selected examples of lactam-based rigid peptide analogs, see: (a) Rapoport, H.; Wolf, J. P. *J. Org. Chem.* **1989**, *54*, 3164 as well as references 1–8 therein. (b) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104. (c) Freidinger, R. M. *J. Org. Chem.* **1985**, *50*, 3631. (d) Zydowsky, T. M.; Dellaria, J. F., Jr.; Nellans, H. N. *J. Org. Chem.* **1988**, *53*, 5607. (e) Kempf, D. J.; Condon, S. L. *J. Org. Chem.* **1990**, *55*, 1390. (f) Ward, P.; Ewan, G. B.; Jordan, C. C.; Ireland, S. J.; Hagan, R. M.; Brown, J. R. *J. Med. Chem.* **1990**, *33*, 1848. (g) Toniolo, C. *Int. J. Pept. Protein Res.* **1990**, *35*, 287. (h) Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914. (i) Flynn, G. A.; Burkholder, T. P.; Huber, E. W.; Bey, P. *BioMed. Chem. Lett.* **1991**, *1*, 309. (j) Burkholder, T. P.; Huber, E. W.; Flynn, G. A. *BioMed. Chem. Lett.* **1993**, *3*, 231.

(5) (a) Shono, T.; Matsumura, Y.; Inoue, K. *J. Org. Chem.* **1983**, *48*, 1389. (b) Ginzel, K.-D.; Brungs, P.; Steckhan, E. *Tetrahedron* **1989**, *45*, 1691. (c) Moeller, K. D.; Rutledge, L. D. *J. Org. Chem.* **1992**, *57*, 6360.

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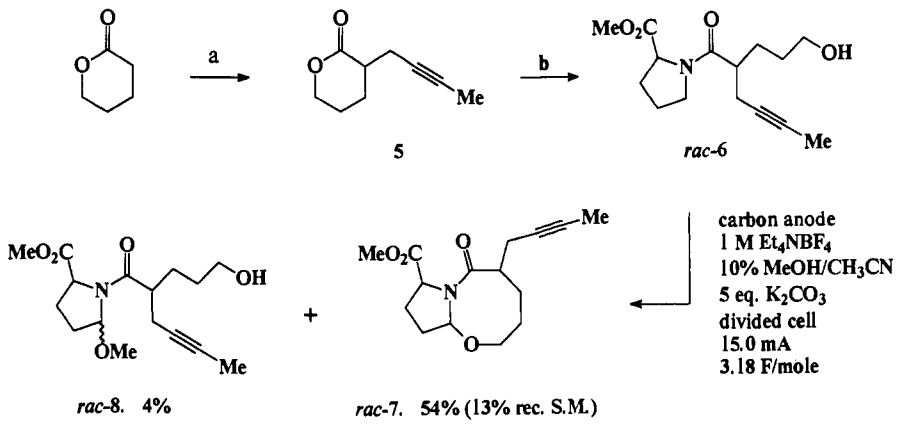
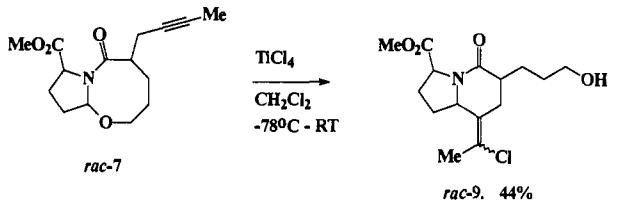
Scheme II[a]



[a] Reagents: (a) i. LDA, THF, –40 °C, ii. 1-bromo-2-butyne, 63%; (b) proline methyl ester hydrochloride, Me_3Al, Et_3N, CH_2Cl_2, reflux, 49%.

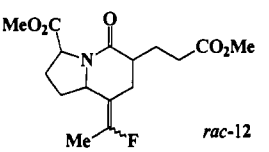
Scheme III



In order to address this question, we undertook the synthesis of angiotensin-converting enzyme (ACE) inhibitors A58365A and A58365B. A58365A (**1a**) and A58365B (**1b**) were first found in the culture filtrate of *Streptomyces chromofuscus* NRRL 15098 and are both effective ACE inhibitors at nanomolar concentrations.[6] The first total synthesis of A58365A was reported by Danishefsky and Fang in 1989.[7] A58365B has not been synthesized to date. These two molecules provided an ideal test for the generality of an electrochemically based annulation procedure for building bicyclic lactam ring skeletons. If such a procedure was effective, then both molecules could be viewed as arising from the exact same synthetic route by simply varying the size of the starting amine (Scheme I). In this scenario, an amino acid derivative containing an acetylene would be selectively oxidized[8] and then the resulting methoxylated amide would be treated with titanium tetrachloride in order to complete the cyclization.[9] We report here the successful completion of the syntheses of both (–)-A58365A[10] and (±)-A58365B.

Initial Studies and Synthesis of (±)-A58365A. The initial substrate for electrolysis (**6**) was synthesized from δ-valerolactone as outlined in Scheme II.[11] A mixture of stereoisomers was obtained. However, this mixture was not a concern since the stereogenic atom on the six-membered ring was not present in the final target molecule. Unknown to us at the time, the trimethylaluminum-catalyzed opening of the alkylated δ-valerolactone **5** racemized the stereogenic atom on the proline ring (*vide infra*). The electrolysis of *rac*-**6** was conducted under constant current conditions (15.0 mA, 3.18 F/mol) using a divided cell, carbon electrodes, a 1 M tetraethylammonium tetrafluoroborate in 10% methanol/acetonitrile electrolyte solution, and 5 equiv of potassium carbonate as a proton scavenger. A 54% isolated yield of bicyclic ether *rac*-**7** was obtained along with a 4% yield of the methoxylated amide product *rac*-**8** and a 13% yield of the recovered starting material. The formation of the eight-membered ring ether did not interfere with the completion of the annulation procedure (Scheme III). Treatment of compound *rac*-**7** with titanium tetrachloride in dichloromethane led to a 44% unoptimized yield of the desired bicyclic vinyl chloride *rac*-**9**.

Although these initial experiments were promising, problems associated with the isolation of bicyclic ether *rac*-**7** from the crude oxidation mixture and the poor yield obtained for the titanium-tetrachloride-catalyzed cyclization of *rac*-**7** led us to consider changing the substrate for the electrolysis in order to encourage the formation of a methoxylated product during the oxidation reaction. To this end, alcohol *rac*-**6** was oxidized with Jones reagent and the resulting acid esterified with *N,N*-dimethylformamide dimethyl acetal[12] in refluxing benzene to afford a 93% yield of an electrolysis substrate (**10**) having a methyl ester on the side chain. The initial attempt to oxidize substrate *rac*-**10** utilized conditions that were nearly identical to those used with substrate *rac*-**6**. In this case, a 56% isolated yield of the methoxylated product *rac*-**11** (Scheme IV) was obtained along with a 17% yield of the recovered starting material. The methoxylated product was isolated from this reaction by adding triethylamine to the crude anolyte, removing the solvent *in vacuo*, and immediately chromatographing the product through silica gel. When triethylamine was not added, concentration of the crude reaction mixture led to the formation of two isomeric bicyclic vinyl fluorides *rac*-**12**. The two vinyl fluorides, which were



tentatively identified by ^1H NMR, ^{13}C NMR, ^{19}F NMR, and GCMS, were isolated in addition to a complex mixture of other unidentifiable products. The vinyl fluoride products were not stable (*vide infra*). The formation of the vinyl fluorides was attributed to the formation of tetrafluoroboric acid upon concentration.[13]

Efforts to optimize the yield of the anodic oxidation reaction included varying the solvent, supporting electrolyte, temperature, electrodes, current density, and type of cell. In contrast to earlier

(6) For the isolation and characterization of **1a** and **1b**, see: Mynderse, J. S.; Samlaska, S. K.; Fukuda, D. S.; DuBus, R. H.; Baker, P. J. *J. Antibiot.* **1985**, *38*, 1003. Hunt, A. H.; Mynderse, J. S.; Samlaska, S. K.; Fukuda, D. S.; Maciak, G. M.; Kirst, H. A.; Occolowitz, J. L.; Swartzendruber, J. K.; Jones, N. D. *J. Antibiot.* **1988**, *41*, 771.

(7) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 3621.

(8) For examples of the selective oxidation of an amide in the presence of both monosubstituted and disubstituted acetylenes, see reference 3k.

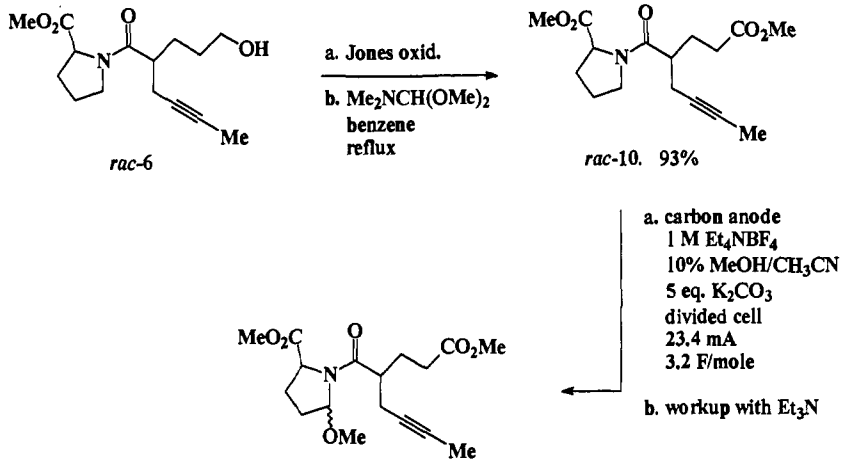
(9) Acetylenes have been reported to be excellent nucleophiles for accomplishing the intramolecular trapping of *N*-acyliminium ions. See: Schoemaker, H. E.; Boer-Terpstra, T. J.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 143.

(10) For a preliminary account of our synthesis of A59365A, see: Moeller, K. D.; Wong, P. L. *BioMed. Chem. Lett.* **1992**, *2*, 739.

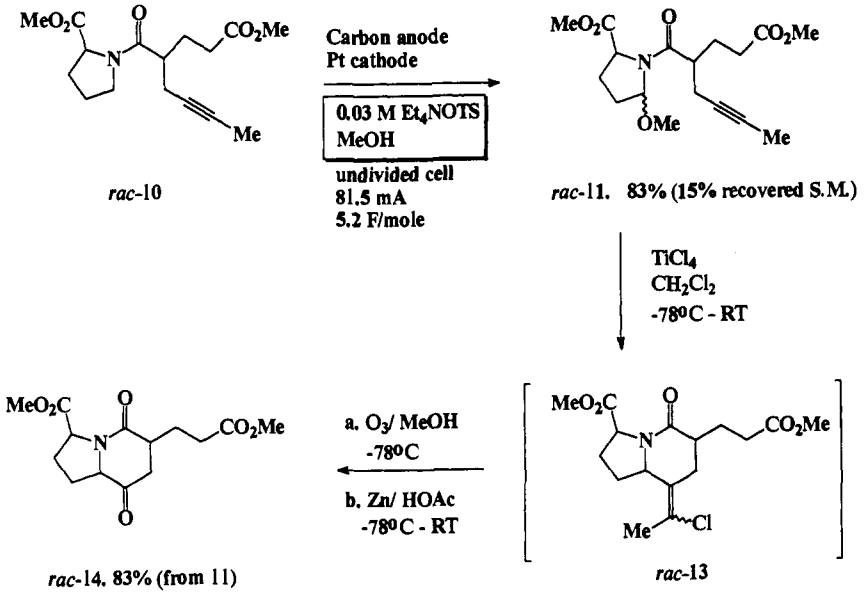
(11) For the use of trimethylaluminum as a catalyst for amide formation, see: (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171. (b) Lipton, M.; Basha, A.; Weinreb, S. M. In *Organic Synthesis*; Coates, R. B., Ed.; John Wiley and Sons, Inc.: New York, 1979; Vol. 59, p 49.

(12) (a) Abdulla, K. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675. (b) Brechbuchler, H.; Buchi, H.; Hatz, E.; Schreiber, J.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 212. (c) Widmer, U. *Synthesis* **1983**, 136.

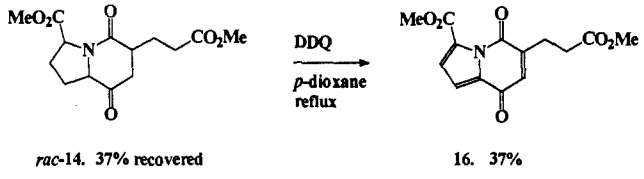
Scheme IV



Scheme V

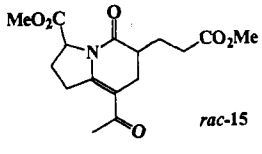


Scheme VI



annulation procedures that benefited from the use of acetonitrile as a cosolvent,[3] the oxidation of *rac*-**10** proceeded best using the electrolysis conditions pioneered by Shono and co-workers.[2c] For example, 3 mmol of *rac*-**10** was oxidized in an undivided cell using constant current conditions (81.5 mA, 5.2 F/mol), a carbon anode, a platinum cathode, and a 0.03 M tetraethylammonium tosylate in methanol electrolyte solution in order to afford an 83% isolated yield of the methoxylated amide *rac*-**11** along with 15% of the recovered starting material (Scheme V). The oxidation was run multiple times on scales ranging from 1 to 11 mmol. The yield of the methoxylated product was always in excess of 70%.

The methoxylated amide *rac*-**11** was treated with titanium tetrachloride in dichloromethane to afford bicyclic vinyl chloride *rac*-**13**. The vinyl chloride proved to be unstable. One of the products obtained from the decomposition of *rac*-**13**, as well as the decomposition of vinyl fluoride *rac*-**12**, was β'-acetyl enamide *rac*-**15**. Apparently, this product arose from migration of the

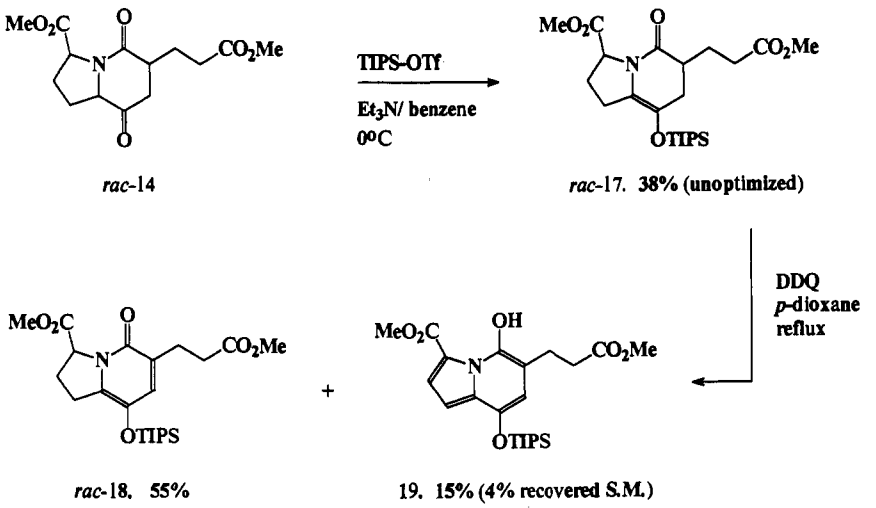


olefin in both *rac*-**12** and *rac*-**13** to form an enamide followed by air oxidation. In order to circumvent this problem, the crude vinyl chloride was immediately ozonolyzed at −78 °C in methanol followed by workup with zinc in acetic acid. An 83% isolated yield of keto amide *rac*-**14** was obtained for the two-step process.

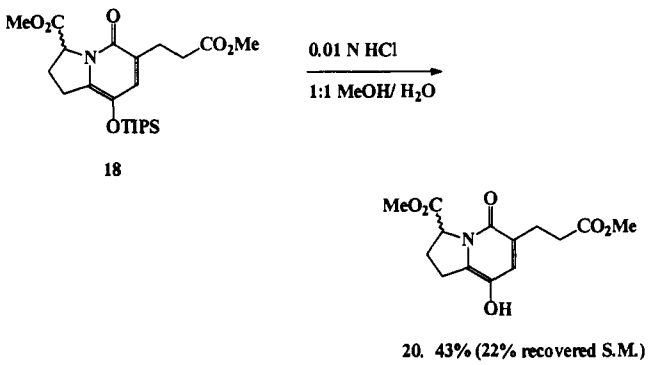
All that remained to complete the synthesis was to oxidize the six-membered ring and hydrolyze the methyl esters. Our initial plan called for a DDQ oxidation of *rac*-**14**. However, when *rac*-**14** was treated with DDQ in refluxing *p*-dioxane, only product **16** was obtained in a 37% isolated yield along with a 37% yield of recovered *rac*-**14** (Scheme VI). Product **16** was envisioned as arising from one of two possible routes. Either the desired product

(13) The feasibility of this reaction was tested by treating *N*-4-hexynoyl-2-methoxypyrrolidine with tetrafluoroboric acid. As with **29**, this reaction led to the formation of a six-membered ring lactam and an exocyclic vinyl fluoride. Interestingly, treatment of *N*-4-pentynoyl-2-methoxypyrrolidine with tetrafluoroboric acid led to the formation of a seven-membered ring lactam as expected[9,3k] and the formation of an endocyclic vinyl fluoride.

Scheme VII



Scheme VIII



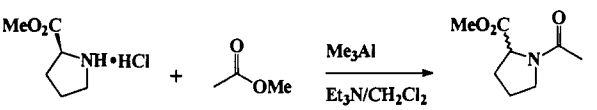
(**20**) had been formed and then undergone a second oxidation reaction or the initial oxidation reaction had led to the radical cation of the amide. Formation of an amide radical cation would be expected to lead to the formation of an iminium ion followed by the elimination of a proton to form an even more readily oxidizable enamide in the five-membered ring. Of these two possibilities, the second seemed most plausible since the amide was the functional group in the molecule with the lowest oxidation potential and since the reaction had led to only the overoxidized product and a substantial recovery of the starting material. In no instance was the desired product observed. In order for this to be the case, the desired product would have to oxidize more readily than the starting material, a situation that was difficult to imagine since the desired product (**20**) would be an aromatic ring.

In order to avoid initial oxidation of the amide and to "channel" the oxidation toward the six-membered ring, an electron-rich functional group was introduced into the six-membered ring of *rac*-**14** (Scheme VII). To this end, ketone *rac*-**14** was treated with triisopropylsilyl triflate and triethylamine to afford triisopropylsilyl enol ether *rac*-**17**.[14] Treatment of *rac*-**17** with DDQ in refluxing *p*-dioxane led to a 55% isolated yield of the desired six-membered ring aromatic compound *rac*-**18** along with a 15% yield of the overoxidized product **19** and 4% of the recovered starting material.

Compound *rac*-**18** was then treated with a solution of 0.01 N HCl in 1:1 methanol/water in order to cleave the triisopropylsilyl ether protecting group and converge on the synthesis of Danishefsky and Fang (Scheme VIII).[7] However, *an optical rotation of* **20** *indicated that the material was racemic*! Compound **18** also proved to be racemic. Clearly, the stereogenic atom initially derived from L-proline methyl ester had been epimerized somewhere during the synthesis.

Total Synthesis of (-)-A58365A. In order to complete an asymmetric synthesis of A58365A, it was imperative to identify the step or steps in the initial synthesis that had led to the epimerization. A series of control experiments were run using *N*-acetyl-L-proline methyl ester as a probe for loss of stereochemistry. For example, the initial finding of Shono concerning the integrity of the stereogenic atom in the oxidation reaction was confirmed by electrolyzing *N*-acetyl-L-proline methyl ester to form the methoxylated amide followed by a reduction of the product with triethylsilane and trifluoroacetic acid in chloroform (Scheme IX).[15] In this experiment, none of the chirality of the initial starting material was lost. The titanium tetrachloride reaction also proved to be innocuous. When the methoxylated amide **22** was subjected to the normal titanium tetrachloride cyclization conditions followed by the addition of water to form the hydroxylated amide **23** and reduction with triethylsilane and trifluoroacetic acid in chloroform, the *N*-acetyl-L-proline methyl ester obtained was recovered without a loss in stereochemistry. In a similar fashion, the Jones oxidation and the formation of the silyl enol ether steps were shown to not lead to any measurable epimerization.

However, the trimethylaluminum-catalyzed amide formation reaction used to open the alkylated δ-valerolactone in the second step of the synthesis was shown to lead to complete epimerization of the L-proline methyl ester starting material.



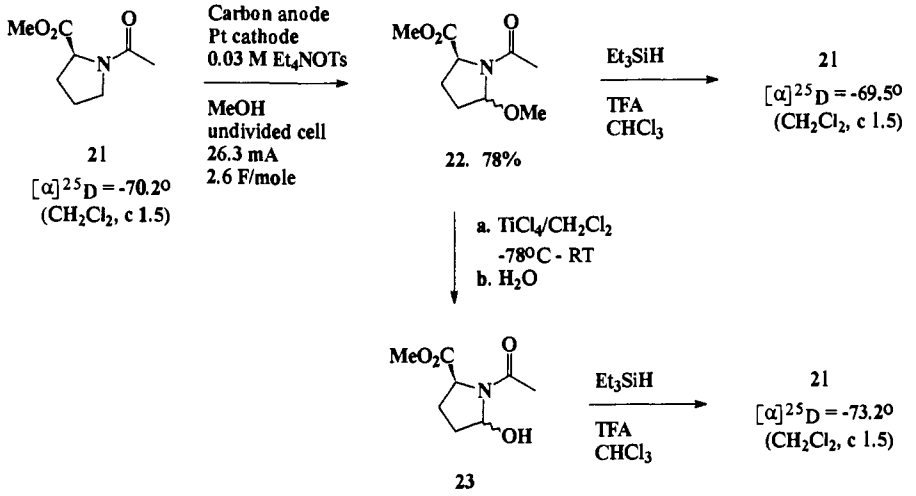
$[\alpha]^{25}_D = +0.86°$ (CH_2Cl_2, c 1.5)

Epimerization at this stage of the synthesis was easily avoided by opening the lactone with (S)-(+)-2-pyrrolidinemethanol instead of L-proline methyl ester in order to form diol **24** (Scheme X). Diol **24** was then treated with Jones reagent followed by *N*,*N*-dimethylformamide dimethyl acetal in order to form diester substrate **10** with the stereogenic atom on the proline ring intact. The synthesis was then completed in a fashion identical to the one described earlier for the racemic material (Scheme XI). Compound **20** gave rise to a rotation of $[\alpha]^{21}_D = -169.6°$ (CH_2Cl_2, *c* 1.5). The literature value for the rotation of **20** is $[\alpha]^{25}_D = -184.8°$ (CH_2Cl_2, *c* 1.5).[7] The difference in the observed and literature values for the optical rotation of **20** indicated that the stereogenic atom on the pyrrolidine ring had undergone a small

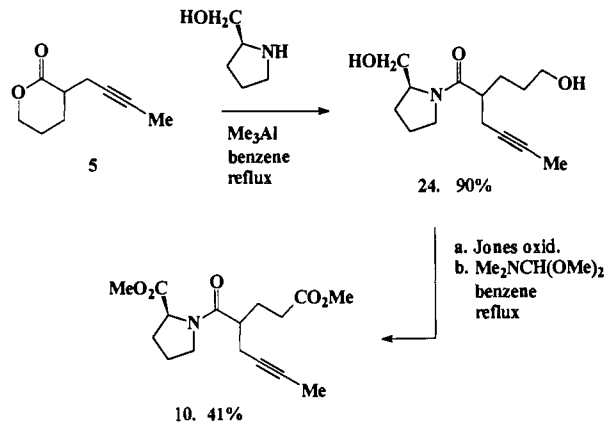
(14) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(15) Hart, D. J.; Cain, P. A.; Evans, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 1548.

Scheme IX



Scheme X



amount of epimerization during the synthesis. The difference in rotation would suggest that the synthesis was completed with an overall enantiomeric excess of approximately 92%.

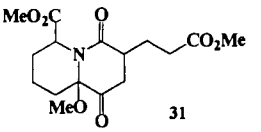
This synthesis clearly demonstrated that an anodic amide-oxidation-based strategy for annulating lactam rings onto amines could provide a convenient route into the 1-aza-2-oxobicyclic-[4.3.0]nonane ring skeleton found in A58365A.

Total Synthesis of (±)-A58365B. Our initial premise was that if the anodic amide-oxidation-based annulation procedure was general, then both A58365A and A58365B could be synthesized using identical chemistry except for the size of the starting amine. In order to test this hypothesis, we undertook an effort to repeat the synthesis outlined above using *d,l*-2-piperidinemethanol as the starting material. The racemic material was used because of the cost associated with the L-pipecolic acid ($100/g) needed for making the chiral starting material.[16]

The substrate for the anodic amide oxidation reaction (**25**) was prepared using the same chemistry as described above for the preparation of substrate **10** (Scheme XII). The anodic amide oxidation, the titanium tetrachloride cyclization, and the ozonolysis reaction were all done in an identical fashion to those in the synthesis of A58365A. The only difference was that in this case the methoxylated amide from the anodic oxidation reaction could not be readily separated from the recovered starting material (**25**). For this reason, the crude methoxylated amide was cyclized using titanium tetrachloride and then treated under the ozonolysis conditions. The material was purified after the three-step sequence. A 74% isolated yield of **27** was obtained. Once again, the annulation procedure worked extremely well! The product obtained was a mixture of three isomers that were isolated in two fractions having a 2:3 ratio. For convenience, the minor isomer that eluted faster by TLC will be called **27a** and the two slower isomers that were isolated together will be called **27b**.

At this point, we envisioned converting both **27a** and **27b** into the final product using the chemistry developed in connection with the conversion of **14** into A58365A. No problems were anticipated with this transformation because of the close similarity of **27a** and **27b** to **14**. However, we were in for quite a surprise. When **27a** was treated with triisopropylsilyl triflate and triethylamine in benzene, only the starting material was recovered. Interestingly, when **27a** was treated with DDQ, no reaction occurred. This was again in contrast to the reactivity of **14**. To make matters worse, when **27a** was treated with the sterically smaller *tert*-butyldimethylsilyl triflate and triethylamine in benzene, the starting material was consumed but none of the desired product (**28**) was obtained (Scheme XIII). Instead, a 21% yield of regio isomeric silyl enol ether **29a** was obtained along with a 66% yield of the bridged tricyclic product **30a**. The assignment of product **30a** eluded us for quite some time. Eventually, it was solved with the use of a combination of HMQC-TOCSY and HMBC NMR experiments.[17] These two experiments allowed us to assign the complete C–C and C–H bond connectivity of the molecule. The stereochemistry at C_{10} and C_{12} was not determined.

Attempts to oxidize **29a** with DDQ in *p*-dioxane or with the use of palladium acetate in acetonitrile met with failure. At this point, it was clear that a new approach to completing the synthesis of A58365B was needed. A number of methods aimed at raising the overall functionality of **27a** and **27b** were tried, including an electrochemical oxidation reaction. Most of these methods were not successful. The electrochemical oxidation (constant current of 24 mA, carbon anode, platinum cathode, 0.03 M tetraethylammonium tosylate in methanol electrolyte solution, and undivided cell) did lead to the desired methoxylated products **31**, but the yields were not acceptable. For example, the anodic oxidation of **27b** afforded only a 7% yield of **31b**.



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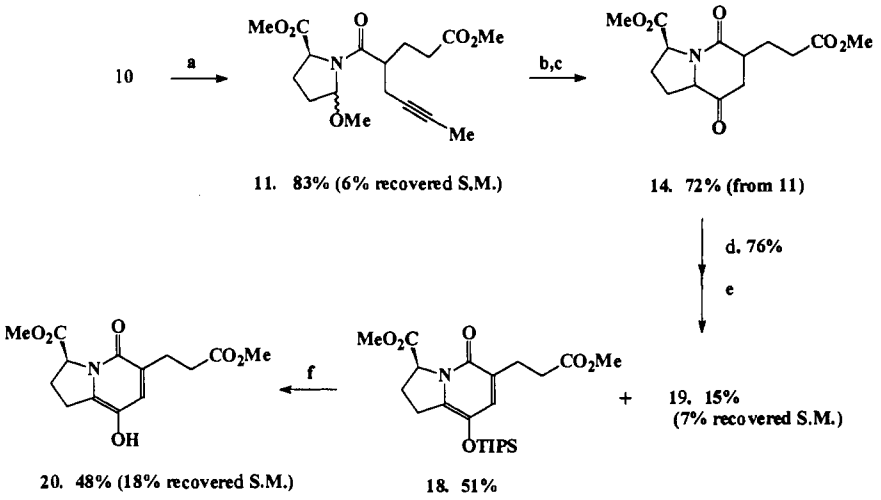
The net oxidation of **27a** and **27b** could be accomplished with a selenylation–dehydroselenylation sequence. In order to initiate this transformation, **27a** and **27b** needed to be selectively

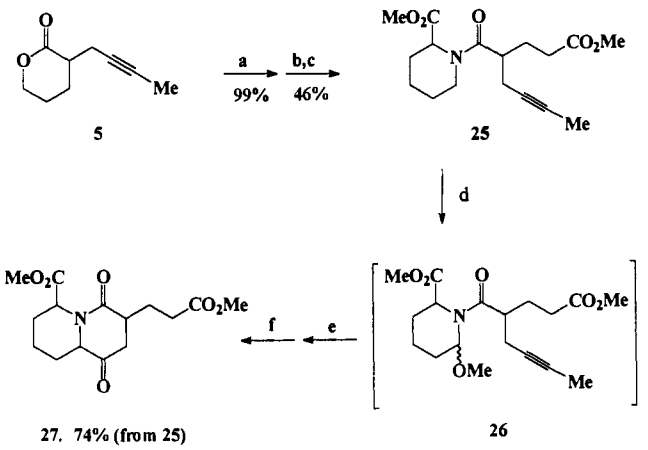
(16) L-Pipecolic acid can be made in reasonable yield from L-lysine and disodium nitrosylpentacyanoferrate(II); see: Kisfaludy, L.; Korenczki, F. *Synthesis* **1982**, 163. This route was used to prepare some of the pure (*S*)-(+)-piperidinemethanol (following subsequent $LiAlH_4$ reduction of the L-pipecolic acid). However, P.L.W. experienced major chest discomfort during the preparation of the L-pipecolic acid even when the reaction was run in the hood. Therefore, this route was abandoned.

Scheme XI[a]



[a] Reagents: (a) carbon anode, Pt cathode, 0.03 M Et_4NOTs in MeOH, undivided cell, 36.0 mA, 6.5 F/mol; (b) $TiCl_4$, CH_2Cl_2, −78 °C to room temperature; (c) i. O_3, MeOH, −78 °C, ii. Zn, HOAc, −78 °C to room temperature; (d) TIPS–OTf, Et_3N, benzene, 0 °C to room temperature; (e) DDQ, *p*-dioxane, reflux; (f) 0.01 N HCl in 1:1 MeOH/H_2O.

Scheme XII[a]



[a] Reagents: (a) 2-piperidinemethanol, Me_3Al, benzene, reflux; (b) Jones oxidation; (c) $Me_2NCH(OMe)_2$, toluene, reflux; (d) carbon anode, Pt cathode, 0.03 M Et_4NOTs in MeOH, 35.4 mA, 5.2 F/mol; (e) $TiCl_4$, CH_2Cl_2, −78 °C to room temperature; (f) i. O_3, MeOH, −78 °C, ii. Zn, HOAc, −78 °C to room temperature.

deprotonated at the methylene α to the ketone (C_4; see Scheme XIV for numbering), especially if the synthesis was to be used at a later date to construct A58365B in an asymmetric fashion. The selectivity of the required deprotonation reaction was examined by treating **27b** with lithium diisopropylamide in THF at −78 °C and then quenching the reaction with methanol-d_4. The starting material and the product were then carefully examined by ^1H and ^2H NMR. The complete C–H and C–C connectivity of the starting material was determined with the use of an HMQC–TOCSY experiment. When the ^1H NMR spectrum of the deuterated product was compared to the ^1H NMR spectrum of the starting material, it was clear that only the C_4 methylene protons had been significantly reduced in size. This result was confirmed by the appearance of a triplet at δ 40.2 (adjacent to the δ 40.5 signal assigned to C_4 in the starting material) in the ^{13}C NMR spectrum. The possibility of deuterium incorporation elsewhere in the molecule was examined by ^2H NMR. Four signals were seen. As expected, the two major signals observed corresponded to deuterium incorporation at C_4. One of the smaller signals (less than 9% by integration) corresponded to deuterium incorporation at C_6. The final signal (about 7% *vs* incorporation at C_4 by integration) corresponded to the incorporation of a deuterium at C_{10} of the starting material. The selectivity of the deprotonation suggested that the reaction would be compatible with an asymmetric synthesis but that some of the chirality would be lost. If needed, the selectivity of the deprotonation step could most likely be improved further with the use of a more sterically hindered base.

With this information in mind, we treated ketone **27b** with LDA in THF at −78 °C and then quenched the resulting enolate with benzene selenenyl bromide (Scheme XIV). A disappointing 16% yield of the selenated product **32b** was obtained along with 23% of the unreacted starting material. The yield of the reaction did improve with the use of a sterically more hindered base. When the reaction was repeated with the use of lithium 2,2,6,6-tetramethylpiperidide as the base, a 45% yield of the selenation product **32b** was obtained along with a 14% yield of the recovered starting material. When **27a** was treated under the same conditions, a 48% yield of **32a** was obtained along with 14% of the unreacted starting material. Treatment of either **32a** or **32b** with MCPBA led to the formation of product **33** in 54% and 48% yield, respectively. Apparently, this product arose from overoxidation of the desired aromatic product **34**. The overoxidation could not be stopped. When less than 2 equiv of MCPBA was used, a mixture of the starting selenide and the overoxidized product was obtained. In no case was the desired product observed. The use of hydrogen peroxide, ozone, and (+)-(8,8-dichlorocamphorsulfonyl)oxaziridine all led to the overoxidized product.

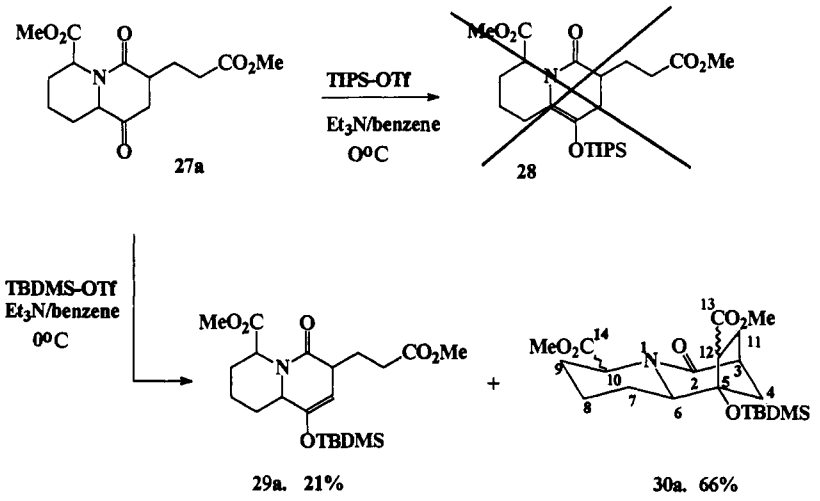
Fortunately, the overoxidized product could be readily reduced back to the desired aromatic product **34**. Treatment of **33** with triethylsilane and trifluoroacetic acid in chloroform led to a 99% isolated yield of **34**. The synthesis of A58365B was completed by treatment of **34** with 9 M HBr and tetrabutylammonium bromide at 110 °C. An 85% yield of the natural product was obtained.

Conclusions

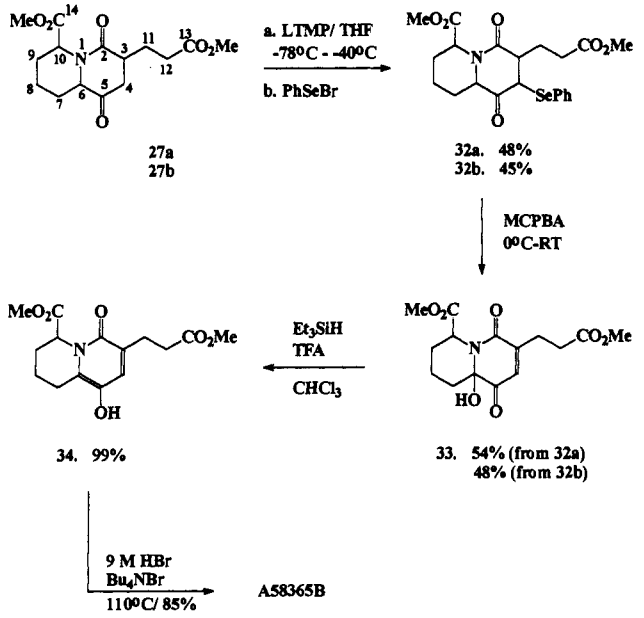
In the end, both A58365A and A58365B were constructed using an anodic amide-oxidation-based procedure for annulating lactam rings onto amino acid derivatives. Although it proved impossible to make both molecules by identical synthetic routes, the differences in the synthesis were not encountered during the

(17) For descriptions of the use of HMQC–TOCSY and HMBC experiments, see: (a) Martin, G. E.; Crouch, R. C. *J. Nat. Prod.* **1991**, *54*, 1. (b) Spitzer, T. D.; Crouch, R. C.; Martin, G. E.; Sharaf, M. H. M.; Schiff, P. L., Jr.; Tackie, A. N.; Boye, G. L. *J. Heterocycl. Chem.* **1991**, *28*, 2065. (c) Spitzer, T. D.; Crouch, R. C.; Martin, G. E. *J. Heterocycl. Chem.* **1992**, *29*, 265. (d) Castle, L. W.; Johnston, M. D., Jr.; Camoutsis, C. L.; Castle, R. N. *J. Heterocycl. Chem.* **1992**, *29*, 1805.

Scheme XIII



Scheme XIV



annulation procedure. In fact, the anodic amide oxidation reaction proceeded in high yield under identical conditions in both syntheses. The success of these two syntheses serves to highlight the general utility of anodic amide oxidations for the construction of bicyclic lactam peptide mimetics. Efforts to employ these reactions in the synthesis of computer-designed peptide mimetics are currently underway.

Experimental Section[18]

General Data. Proton magnetic resonance spectra were recorded using a Varian Gemini 300, Varian XL-300, Varian XR-500, or Varian Unity 600 spectrometer. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane in δ units, and coupling constants are given in cycles per second (hertz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; and m, multiplet. Carbon spectra were obtained using either the Gemini 300 at 75 MHz or Varian XR-500 spectrometer at 126 MHz and are reported in ppm with the center line of the triplet at 77.00 ppm for chloroform-*d* or with the center line of the triplet at 128.00 ppm for benzene-d_6. Routine ^{13}C NMR spectra were fully decoupled by broad-band Waltz decoupling. The ^2H NMR spectrum was obtained using a Varian XL-300 spectrometer in chloroform-*d*. ^{19}F NMR spectra were obtained using a Varian XL-300 spectrometer in chloroform-*d* and are reported in ppm relative to the singlet at 76.53 ppm for trifluoroacetic acid. Two-dimensional NMR experiments (HMQC, HMQC–TOCSY, and HMBC) were performed either on the Varian XR-500 or Varian Unity 600 spectrometer equipped with a reverse detection probe. In these experiments, the ^1H 90° pulse width of 7.5 (XR-500) and 11.5 μs (Unity 600) and a preacquisition delay of 2 s were used. HMQC, HMQC–TOCSY, and HMBC data were acquired at 4, 16, and 64 transients per evolution period increment, respectively. ^{13}C Waltz decoupling was used over a bandwidth of 22 × 10^3 Hz, and 150 evolution increments were used in the t_1 (^{13}C) domain. The sweep width used in ^1H dimension were *ca.* 3945.6 and 4734.7 Hz for the Varian XR-500 and Varian Unity 600 instruments, respectively. The sweep width used in ^{13}C dimension were *ca.* 13 000 and 15 600 for the Varian XR-500 and Varian Unity 600 instruments, respectively, with 2048 complex data points collected in the t_2 (^1H) domain. An isotropic mixing time period of 15 ms was used in the HMQC–TOCSY experiments. A focusing delay period for multiple H–C bond coherence of 55 ms was used in HMBC experiments. HMQC and HMQC–TOCSY processing used a Gaussian filter in both t_1 and t_2 with zero filling to 1024 data points in t_1. HMBC processing used an absolute value "pseudoecho" weighting in t_2 and Gaussian filtering in t_1. Infrared spectra (IR) were obtained using either a Perkin-Elmer 283B or a Mattson Polaris FT-IR spectrophotometer. UV spectra were obtained using a Perkin-Elmer Lambda 3A spectrophotometer. Optical rotation measurements were performed on a Perkin-Elmer 241 digital polarimeter using a 10-cm cell. Low-resolution mass spectral data were obtained on a Finnigan 3200 GC/MS or Finnigan 3300 GC/MS spectrometer. High-resolution mass spectral data were obtained using a VG ZAB-SE MS spectrometer with an 8-keV xenon FAB source. Carbon, hydrogen, and nitrogen analyses were obtained from Oneida Research Services, Inc., Whitesboro, NY.

Gravity-flow chromatography was accomplished by using E. Merck silica gel 60 (70–230 mesh). HPLC was accomplished using an SSI system including a Model 222C pump, a Model 500 detector, and Axxiom 727 control and integration software. Analytical HPLC work was performed using a 4.6-mm × 25 cm XPERTEK ODS column from P. J. Cobert. Semipreparative HPLC separations utilized a 9-mm × 50-cm Whatman Magnum 9 ODS-3 column. Reactions were monitored as a function of time by TLC with E. Merck silica gel 60 F_{254} plates, E. Merck RP-18 F_{254} glass plates, or capillary GC. The solvents used for chromatography were mixed by volume and are reported for each experiment. Capillary GC data were obtained using a HP Model 5890A instrument equipped with a HP 3396A integrator and a HP 20-m ULTRA II (5% phenyl methyl silicone) column.

Preparative electrolyses were conducted using a Model 630 coulometer, a Model 410 potentiostatic controller, and a Model 420A power supply purchased from The Electrosynthesis Co., Inc. Carbon rods and platinum electrodes were also purchased from The Electrosynthesis Co., Inc. Tetraethylammonium tosylate was purchased from Aldrich and stored in a vacuum desiccator (*ca.* 0.5 mmHg). Tetrabutylammonium tetrafluoroborate was purchased from Aldrich and used without purification. Anhydrous methanol was purchased from Aldrich in Sure/Seal bottles and used without further purification.

Ozonolysis was accomplished using the Welsbach ozonator T-816 from The Welsbach Corp.

(18) Where there is overlap, only experimentals for the asymmetric synthesis of A58365A are given. The experimentals for the racemic synthesis are, for all practical purposes, identical.

Chemical reagents and starting materials were purchased from Aldrich and used without purification unless otherwise noted. *n*-Butyllithium was purchased both as a 2.5 and 1.6 M solution in hexanes. Trimethylaluminum was purchased both as a 2.0 M solution in toluene and a 2.0 M solution in dichloromethane. Titanium(IV) chloride was purchased as a 1.0 M solution in dichloromethane. δ-Valerolactone was purchased from Lancaster. Diisopropylamine and 2,2,6,6-tetramethylpiperidine were distilled from calcium hydride. Triethylamine was distilled from molecular sieves (3A). Oxalyl chloride was freshly distilled before use. *N,N*-Dimethylformamide was distilled over calcium hydride. 1-Bromo-2-butyne was prepared from 2-butynol and phosphorus tribromide using the procedure of Schulte and Reiss.[19] Jones reagent was prepared by dissolving 13.4 g of chromium(VI) oxide in 12 mL of concentrated sulfuric acid and diluting to 100 mL with water. *N*-Acetylpyrrolidine was purchased from American Biorganics, NY, and used without purification. Zinc dust and sodium methoxide were purchased from Fisher.

All solvents used for synthesis were distilled before use. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Acetonitrile, benzene, dichloromethane, and toluene were distilled from calcium hydride. *p*-Dioxane was distilled from lithium aluminum hydride. Chloroform was purified by washing with water, drying over calcium chloride, and distilling over calcium chloride. Chloroform-*d* was purchased from Cambridge Isotope Laboratories (CIL) and used without further purification.

All reactions were run under an inert atmosphere of nitrogen in flame-dried glassware unless specified otherwise.

The purity of all compounds was determined by either C, H, and N analyses or proton and carbon NMR (>90–95%) data.[20]

2-(2-Butynyl)-δ-valerolactone (5). To a stirred solution of 33.4 g (330 mmol) of diisopropylamine in 250 mL of tetrahydrofuran at –40 °C was added dropwise 120 mL (300 mL) of a 2.5 M *n*-butyllithium in hexane solution. After 30 min, a solution of 30.0 g (300 mmol) of δ-valerolactone in 200 mL of tetrahydrofuran was added dropwise and the solution was stirred for 1.5 h at –45 °C. 1-Bromo-2-butyne (48.0 g, 360 mmol) was then added in one portion, and the solution was stirred at –45 °C for 4 h. The reaction mixture was then poured into a 2-L separatory funnel containing 1 L of wet ether and 150 mL of saturated aqueous ammonium chloride solution. The organic layer was separated and washed with saturated aqueous ammonium chloride solution (2 × 150 mL). The aqueous solution was extracted with ether (3 × 150 mL). The combined organic layers were washed with water (1 × 150 mL) and saturated aqueous sodium chloride solution (1 × 150 mL), dried over sodium sulfate, and concentrated *in vacuo*. The crude mixture was chromatographed through 500 g of silica gel that was slurry-packed with a 35% ether/hexane solution containing 0.2% triethylamine. Gradient elution from 35% ether/hexane to 45% ether/hexane afforded 28.6 g (63%) of compound **5** as a clear colorless oil. The spectral data are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41–4.30 (m, 2 H), 2.71–2.57 (m, 2 H), 2.52–2.42 (m, 1 H), 2.33–2.22 (m, 1 H), 2.00–1.90 (m, 2 H), 1.79 (apparent t, J = 2.5 Hz, 3 H), 1.77–1.63 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 77.6, 75.7, 68.7, 39.2, 24.0, 21.8, 20.9, 3.2; IR (neat, NaCl) 2953, 2920, 2236, 1734, 1437, 1399, 1352, 1262, 1158, 1084, 977 cm^{-1}; GCMS (PCI) *m/e* (rel. intensity) 181 (M + 29, 11), 153 (M + 1, 100), 125 (M + 1 – CO, 8), 109 (21), 107 (13), 101 (7), 93 (5), 81 (11), 71 (5); HRMS (EI) *m/e* calcd for $C_9H_{12}O_2$ 152.0837, found 152.0837.

Methyl *N*-(2-(3-Hydroxypropyl)-4-hexynoyl)prolinate (*rac*-6). To a 0 °C solution containing 0.427 g (2.57 mmol) of L-proline methyl ester hydrochloride, 0.26 g of triethylamine, and 5 mL of dichloromethane was added 2.60 mL of a 2.0 M trimethylaluminum in dichlormethane solution. The reaction was stirred at room temperature for 15 min, and then, a solution of 0.316 g (2.07 mmol) of **5** in 5 mL of dichloromethane was added. The resulting solution was stirred at room temperature for 24 h and then refluxed for 48 h. The reaction was cooled, and a 30% (w/w) sodium potassium tartrate solution was added cautiously. The resulting two-phase mixture was stirred vigorously until the two phases were clear. The aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude product was chromatographed through 50 g of silica gel that was slurry-packed with ether. Gradient elution from ether to 10% methanol/ether afforded 0.219 g (49%) of *rac*-**6** as the desired product. The spectral data are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88–4.85 (m, 0.28 H), 4.50 (dd, J = 8.4, 3.7 Hz, 0.72 H), 3.86–3.77 (m, 1 H), 3.77 and 3.72 (2 s, total of 3 H), 3.66–3.55 (m, 3 H), 2.78–2.66 (m, 1 H), 2.52–2.40 (m, 1 H), 2.30–1.94 (m, 6 H), 1.80 and 1.76 (2 t, J = 2.5 Hz, total of 3 H), 1.62–1.44 (m 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 173.4, 76.7, 62.2, 58.6, 52.1, 47.1, 42.8, 29.6, 29.0, 28.2, 24.7, 20.1, 3.2; IR (neat, NaCl) 3396 (br), 2954, 2922, 2879, 1740, 1626, 1448, 1339, 1283, 1199, 1180, 1054 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 310 (M + 29, 8), 282 (M + 1, 58), 280 (M$^+$ – H, 4), 264 (M$^+$ – OH, 8), 250 (M$^+$ – OCH_3, 4), 152 (M$^+$ – $C_6H_{10}NO_2$, 7), 131 (7), 130 (100), 128 ($C_6H_{10}NO_2$, 21), 83 (4), 70 (18); HRMS (EI) *m/e* calcd for $C_{15}H_{23}NO_4$ 281.1627, found 281.1627. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24;; N, 4.98. Found: C, 64.02; H, 8.22; N, 5.10.

1-Aza-7-oxa-3-(2-butynyl)-11-carbomethoxy-2-oxobicyclo[6.3.0]undecane (*rac*-7). A 1 M solution of tetrabutylammonium tetrafluoroborate in 10% methanol/acetonitrile was prepared and degassed for 5 min by sonication. A portion of the solution (5 mL) was transferred by syringe to the cathodic chamber of a standard H-cell. To the anodic chamber were added 0.103 g (0.365 mmol) of *rac*-**6**, 0.25 g of anhydrous potassium carbonate as an acid scavenger, and 5 mL of the electrolyte solution. The anodic and cathodic chambers were each equipped with a carbon rod electrode. The reaction was electrolyzed at a constant current of 15.0 mA and monitored by TLC. After 3.18 F of charge had been passed, the anolyte was filtered and diluted with ether. The organic layer was washed four times with an ice-cold solution of saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was chromatographed through 50 g of silica gel that was slurry-packed with a 50% ether/hexane mixture. Gradient elution from 50% ether/hexane to 5% methanol/ether afforded 0.0544 g (54%) of *rac*-**7** (in a ratio of 54:46 of major:minor isomers) and 0.0133 g (13%) of recovered *rac*-**6**. The spectral data for the major isomer are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51 (d, J = 4.8 Hz, 1 H), 4.48 (dd, J = 9.9, 1.5 Hz, 1 H), 3.93–3.74 (dd of an AB pattern, J_d = 7.2 Hz, J_d = 1.5 Hz, ν_A = 1167 Hz, ν_B = 1135 Hz, J_{AB} = 12.5 Hz, 2 H), 3.72 (s, 3 H), 3.14–3.04 (m, 1 H), 2.55 (dp, J = 15.5, 2.6 Hz, 1 H), 2.51–2.30 (m, 3 H), 2.22–2.04 (m, 2 H), 1.97 (t, J = 6.4 Hz, 1 H), 1.93–1.85 (m, 2 H), 1.80 (t, J = 2.4 Hz, 3 H), 1.58 (tt, J = 12.9, 4.8 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 173.9, 173.0, 88.3, 78.2, 77.0, 68.7, 58.8, 51.8, 41.5, 33.1, 33.0, 28.3, 26.9, 22.5, 3.5; IR (neat, NaCl) 2954, 2922, 2858, 2746, 1653, 1428, 1364, 1336, 1307, 1275, 1200, 1177, 1095, 1083, 1065, 1022 cm^{-1}; GCMS (35 eV) *m/e* (rel. intensity) 279 (M$^+$, 2), 220 (M$^+$ – $COOCH_3$, 9), 153 (18), 129 (7), 128 ($C_6H_{10}NO_2^+$, 93), 93 (12), 91 (8), 81 (6), 79 (12), 69 (10), 68 (100), 67 (16), 55 (9); HRMS (EI) *m/e* calcd for $C_{15}H_{21}NO_4$ 279.1470, found 279.1468. The spectral data for the minor isomer are as follows: ^{1}H NMR 300 MHz, $CDCl_3$) δ 5.45 (d, J = 4.2 Hz, 1 H), 4.42 (dd, J = 9.6, 8.1 Hz, 1 H), 4.13 (dd, J = 13.2, 8.4 Hz, 1 H), 3.82 (dd, J = 13.1, 7.1 Hz, 1 H), 3.76 (s, 3 H), 3.05–2.95 (m, 1 H), 2.56 (d of sextet, J = 16.8, 2.6 Hz, 1 H), 2.36–2.23 (m, 3 H), 2.21–1.99 (m, 4 H), 1.90–1.80 (m, 1 H), 1.77 (t, J = 2.6 Hz, 3 H), 1.65–1.59 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 172.5, 87.0, 78.4, 76.3, 68.5, 59.6, 51.5, 41.8, 33.6, 27.4, 26.8, 22.4, 3.5; IR (neat, NaCl) 2952, 2920, 2857, 1751, 1653, 1456, 1429, 1339, 1278, 1197, 1176, 1083 cm^{-1}; GCMS (35 eV) *m/e* (rel. intensity) 279 (M$^+$, 2), 220 (M$^+$ – $COOCH_3$, 11), 153 ($C_9H_{13}NO_2^+$, 19), 129 (11), 128 ($C_6H_{10}NO_2^+$, 100), 98 (27), 93 (11), 91 (10), 79 (11), 71 (10), 69 (10), 68 (87), 67 (14); HRMS (EI) *m/e* calcd for $C_{15}H_{21}NO_4$ 279.1470, found 279.1479.

2-(Hydroxymethyl)-*N*-(2-(3-hydroxypropyl)-4-hexynoyl)pyrrolidine (24). To a solution of 0.260 g (2.53 mmol) of L-prolinol in 5 mL of toluene at 0 °C was added dropwise 1.30 mL (2.53 mmol) of a 2.0 M trimethylaluminum in toluene solution. After the mixture was stirred at room temperature for 45 min, a solution of 0.327 g (2.15 mmol) of 2-(2-butynyl)-δ-valerolactone (**5**) in 5 mL of toluene was added. The resulting solution was refluxed for 2 h and cooled to room temperature, and 10 mL of a 30% (w/w) sodium potassium tartrate solution was slowly added. The mixture was vigorously stirred for 0.5 h and poured into a separatory funnel to separate the organic layer. The aqueous layer was extracted with dichloromethane (5 × 15 mL). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo*, and immediately chromatographed through 60 g of silica gel that was slurry-packed with a 10% methanol/ether solution. Elution with 10% methanol/ether afforded 0.490 g (90%) of the desired product **24**. The spectral data for a mixture of stereoisomers are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22, 4.95, 4.65, 3.90 and 3.07 (br humps, OH protons), 5.54–5.46 (m, 0.1 H), 4.38–4.16 (m, 0.9 H), 3.81 (dt, J = 9.9, 6.5 Hz, 0.5 H), 3.72–3.48 (m, 6.5 H including OH protons), 2.96–2.70 (m, 1 H), 2.44–2.20 (m, 2.4 H), 2.10–1.82 (m, 2.9 H), 1.80–1.66 (m, including an apparent t, total of 4.3 H), 1.64–1.48 (m, 3.4 H); ^{13}C NMR (75 MHz, C_6D_6) δ 175.9,

(19) Schulte, K. E.; Reiss, K. P. *Chem. Ber.* **1954**, 964.

(20) The ^{1}H NMR and ^{13}C NMR spectra for all compounds without C, H, and N analyses are included in the supplementary material.

175.8, 76.6, 76.5, 76.3, 65.6, 63.5, 61.8, 60.5, 60.1, 58.8, 48.0, 43.3, 43.2, 30.0, 29.9, 29.7, 28.4, 28.3, 27.8, 27.7, 27.5, 24.0, 23.9, 22.5, 21.7, 3.0, 2.9; IR (neat/NaCl) 3427 (br), 3287 (br), 2932, 2878, 2241, 1612, 1455, 1343, 1190, 1159, 1052 cm^{-1}; GCMS (PCI) *m/e* (rel. intensity) 255 (14), 254 (M + 1, 55), 236 (M^+ – OH, 10), 153 ($M^+ - C_5H_{10}NO$, 20), 128 ($C_6H_{10}NO_2^+$, 26), 103 (16), 102 (100), 100 ($C_5H_{10}NO^+$, 13), 85 (8), 71 (9), 70 (38); HRMS (EI) *m/e* calcd for $C_{14}H_{24}NO_3$ (MH^+) 254.1756, found 254.1756; calcd for $C_{13}H_{20}NO_2$ ($M^+ - CH_2OH$) 222.1494, found 222.1531. Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 65.73; H, 9.03; N, 5.42. TLC R_f = 0.26 using 10% methanol/ether.

Methyl *N*-(2-(2-Carbomethoxyethyl)-4-hexynoyl)-L-prolinate (10). To a solution of 0.952 g (3.76 mmol) of **24** in 37 mL of acetone at 0 °C was added dropwise 22 mL of Jones reagent. After the addition was completed, the reaction mixture was stirred at 0 °C for 0.5 h and then at room temperature for 1.5 h. Excess methanol was added until a green color of Cr^{3+} salts persisted. The mixture was decanted and filtered though a plug of glass wool. The acetone in the filtrate was removed *in vacuo*, and the residue was dissolved in water. The aqueous layer was saturated with ammonium chloride and extracted with ethyl acetate (5 × 20 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo* to yield 0.836 g of the crude diacid. *N,N*-Dimethylformamide dimethyl acetal (2.84 g) was added to a solution of 0.836 g of this crude diacid in 6 mL of benzene at 80 °C. The reaction mixture was refluxed for 2.5 h and then cooled to room temperature. The mixture was diluted with ether, poured into a separatory funnel, and washed with water (1 × 10 mL), saturated aqueous sodium bicarbonate solution (2 × 10 mL), and saturated aqueous sodium chloride solution (1 × 10 mL). The organic layer was dried over magnesium sulfate, concentrated *in vacuo*, and immediately chromatographed through 70 g of silica gel that was slurry-packed with a 80% ether/hexane solution. Gradient elution from 80% ether/hexane to ether afforded 0.574 g (49%) of the desired product **10** from diol **24**. The spectral data for mixture of stereoisomers are as follows: ^1H NMR (300 MHz, $CDCl_3$) δ 4.87–4.83 (m, 0.26 H), 4.55 (dd, J = 8.5, 4.5 Hz, 0.09 H), 4.48 (dd, J = 8.4, 3.8 Hz, 0.65 H), 3.78 and 3.72 (2 s, total of 3 H), 3.67 and 3.66 (2 s, total of 3 H), 3.69–3.65 (m, 2 H), 2.86–2.76 and 2.68–2.58 (m, 1 H), 2.51–2.15 (m, 5 H), 2.14–1.90 (m, 5 H), 1.79 (t, J = 2.5 Hz, 1.95 H), 1.75 (t, J = 2.4 Hz, 1.05 H); ^{13}C NMR (75 MHz, C_6D_6) δ 174.2, 173.9, 173.4, 173.2, 172.9, 77.7, 77.6, 77.3, 59.2, 59.1, 51.9, 51.4, 47.3, 47.1, 42.6, 42.5, 31.6, 31.5, 29.4, 29.3, 28.1, 27.2, 25.2, 24.9, 22.5, 22.4, 3.4; IR (neat, NaCl) 2953, 2936, 2880, 1734, 1653, 1436, 1339, 1204 cm^{-1}; GCMS (PCI) *m/e* (rel. intensity) 310 (M + 1, 100), 309 (M^+, 13), 278 ($M^+ - OCH_3$, 47), 250 ($M^+ - COOCH_3$, 7), 181 (27), 149 (11), 130 (21), 128 (27), 70 (8); HRMS (EI) *m/e* calcd for $C_{16}H_{23}NO_5$ 309.1576, found 309.1580. Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.09; H, 7.47; N. 4.45. TLC R_f = 0.36 using ether.

Methyl *N*-(2-(2-Carbomethoxyethyl)-4-hexynoyl)-5-methoxy-L-prolinate (11). An oven-dried vial was fitted with a two-hole rubber stopper equipped with a carbon rod anode and a platinum wire cathode. A syringe needle was pushed though the stopper and used as a nitrogen inlet. The vial was charged with 0.302 g (0.977 mmol) of **10**, 4 mL of anhydrous methanol, and 0.035 g of tetraethylammonium tosylate. The reaction mixture was degassed by sonicating under a slow stream of nitrogen for 5 min. The mixture was then electrolyzed at a constant current of 36.0 mA until 6.54 F of charge had been passed. The reaction was then transferred to a round-bottom flask, concentrated *in vacuo*, and immediately chromatographed through 90 g of silica gel that was slurry-packed with a 60% ether/hexane solution. Gradient elution from 60% ether/hexane to ether afforded 0.276 g (83%) of the desired product **11** and 0.0181 g (6%) of the recovered starting material **10**. The spectral data for a mixture of stereoisomers are as follows: ^1H NMR (300 MHz/$CDCl_3$) δ 5.74 (d, J = 4.7 Hz, 0.12 H), 5.32 (d, J = 4.6 Hz, 0.18 H), 5.30–5.21 (m, 0.70 H), 4.91 (t, J = 8.5 Hz, 0.14 H), 4.61–4.53 (m, 0.61 H), 4.99–4.39 (m, 0.25 H), 3.75, 3.73 and 3.71 (three s, total of 3 H), 3.69, 3.68 and 3.66 (three s, total of 3 H), 3.43, 3.41, 3.35, 3.34 and 3.30 (five s, total of 3 H), 3.00–2.80 (m, 1 H), 2.70–2.20 (m, 5 H), 2.19–1.90 (m, 5 H), 1.81, 1.78 and 1.74 (three t, J = 2.5 Hz, total of 3 H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 174.7, 174.1, 173.8, 172.3, 88.7, 88.6, 88.3, 77.3, 76.3, 75.9, 58.5, 54.0, 53.9, 51.9, 51.8, 51.2, 41.5, 41.1, 30.9, 30.4, 29.1, 28.6, 26.8, 26.7, 25.6, 22.4, 21.6, 3.1; IR (neat/NaCl) 2984, 2964, 2922, 1737, 1661, 1436, 1421, 1368, 1336, 1206, 1179, 1086, 1067, 1044, 913 cm^{-1}; GCMS (PCI) *m/e* (rel. intensity) 308 ($M^+ - OCH_3$, 11), 181 (50), 128 (100); HRMS (EI) *m/e* calcd for $C_{17}H_{25}NO_6$ 339.1682, found 339.1687. Anal. Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.42; N, 4.13. Found: C, 60.35; H, 7.11; N, 3.90; TLC R_f = 0.42 using ether.

1-Aza-9-carbomethoxy-3-(2-carbomethoxyethyl)-2,5-dioxobicyclo-[4.3.0]nonane (14). To a solution of 4.858 g (14.3 mmol) of **11** in 143 mL of dichloromethane at –78 °C was added dropwise 36.0 mL (36.0 mmol) of a 1.0 M titanium(IV) chloride in dichloromethane solution. The reaction was allowed to reach room temperature on its own and stirred for 36 h. The reaction solution was poured into 150 mL of 30% (w/w) sodium potassium tartrate solution. The two-phase mixture was vigorously stirred for 1 h, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (10 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to yield 4.90 g of the desired vinyl chloride. This vinyl chloride was unstable and had to be taken to **14** immediately. A solution of 4.90 g of the crude vinyl chloride in 140 mL of methanol at –78 °C was ozonolyzed for 0.5 h after a blue color was first seen. Nitrogen was then bubbled through the solution for 10 min after the first disappearance of the blue color. Zinc dust (2.20 g) and 5.40 g of acetic acid were then added. The reaction mixture was stirred at room temperature for 48 h and filtered, and the filtrate was concentrated *in vacuo*. The viscous liquid was chromatographed through 225 g of silica gel that was slurry-packed with a 70% ether/hexane solution. Gradient elution from 70% ether/hexane to 10% methanol/ether afforded 3.06 g (72%) of the desired ketone **14**. The spectral data are reported for a mixture of stereoisomers: ^1H NMR (300 MHz/$CDCl_3$) δ 4.65 (dd, J = 7.8, 5.9 Hz, 1 H), 4.33 (t, J = 7.2 Hz, 1 H), 3.77 and 3.76 (2 s, total of 3 H), 3.68 and 3.67 (2 s, total of 3 H), 2.97–2.81 (m, 1 H), 2.77 (d, J = 5.2 Hz, 0.5 H), 2.71 (d, J = 5.3 Hz, 0.5 H), 2.55 (t, J = 7.1 Hz, 2 H), 2.51–2.17 (m, 5 H), 2.04–1.94 (m, 1 H), 1.88–1.72 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 174, 172.4, 170.7, 65.1, 58.3, 52.4, 51.5, 40.3, 38.0, 31.2, 27.5, 24.3, 24.0; IR (neat, NaCl) 2956, 1733, 1663, 1437, 1367, 1204, 1177 cm^{-1}; GCMS (PCI) *m/e* (rel. intensity) 326 (M + 29, 20), 298 (M + 1, 100), 297 (M^+, 11), 266 ($M^+ - OCH_3$, 74), 238 ($M^+ - COOCH_3$, 9), 61 (18); HRMS (EI) *m/e* calcd for $C_{14}H_{19}NO_6$ 297.1212, found 297.1216; TLC R_f = 0.35 using 5% methanol/ether.

1-Aza-5-acetyl-9-carbomethoxy-3-(2-carbomethoxyethyl)-2-oxobicyclo-[4.3.0]non-5-ene (15). The spectral data are as follows: ^1H NMR (300 MHz, $CDCl_3$) δ 4.75 (dd, J = 9.3, 3.2 Hz, 1 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 3.29 (ddd, J = 18.4, 9.1, 3.4 Hz, 1 H), 3.04 (p, J = 9.2 Hz, 1 H), 2.90–2.80 (m, 1 H), 2.65–2.55 (m, 2 H), 2.51 (t, J = 7.4 Hz, 2 H), 2.35–2.28 (m, 1 H), 2.27 (s, 3 H), 2.22–2.09 (m, 2H), 1.88–1.79 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 173.9, 171.5, 171.2, 151.5, 109.2, 58.1, 52.5, 51.5, 39.2, 31.0, 30.4, 28.8, 27.9, 26.1, 24.9; GCMS (PCI) *m/e* (rel. intensity) 352 (M + 29, 15), 326 (5), 325 (28), 324 (M + 1, 100), 293 (8), 292 ($M^+ - OCH_3$, 34), 264 ($M^+ - COOCH_3$, 3), 237 ($M^+ - CH_2CH_2COOCH_3$, 3).

1-Aza-9-carbomethoxy-3-(2-carbomethoxyethyl)-2,5-dioxobicyclo-[4.3.0]non-3,6,8-triene (16). To a solution of 0.454 g (0.153 mmol) of **14** in 2 mL of *p*-dioxane was added 0.069 g of 2,3-dichloro-4,5-dicyanobenzoquinone. The resulting mixture was refluxed for 42 h, cooled to room temperature, and diluted with ether. Yellowish brown solids were removed by filtration, and the filtrate was then concentrated *in vacuo*. The crude mixture was chromatographed through 20 g of silica gel that was slurry-packed with a 70% ether/hexane solution. Gradient elution from 70% ether/hexane to 5% methanol/ether afforded 0.0160 g (37%) of **16** and 0.0167 g (37%) of the recovered starting material **14**. The spectral data are as follows: ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, J = 3.8 Hz, 1 H), 6.80 (d, J = 3.8 Hz, 1 H), 6.71 (s, 1 H), 3.94 (s, 3 H), 3.70 (s, 3 H), 2.92 (t, J = 7.1 Hz, 2 H), 2.69 (t, J = 7.1 Hz, 2 H); IR (neat, NaCl) 3136, 2596, 2855, 1734, 1661, 1623, 1559, 1504, 1435, 1386, 1308, 1255, 1199, 1167, 1122, 866, 824, 759 cm^{-1}; GCMS (PCI) *m/e* (rel. intensity) 320 (M + 29, 8), 292 (M + 1, 38), 291 (M^+, 6), 290 (8), 263 (7), 262 (57), 261 (17), 260 ($M^+ - OCH_3$, 100), 61 (12); HRMS (EI) *m/e* calcd for $C_{14}H_{13}NO_6$ 291.0743, found 291.0732.

1-Aza-9-carbomethoxy-3-(2-carbomethoxyethyl)-2-oxo5-(triisopropylsiloxy)bicyclo[4.3.0]non-5-ene (17). To a solution of 1.501 g (5.05 mmol) of **14** in 10 mL of benzene at 0 °C were added 1.79 g (17.7 mmol) of triethylamine and 5.12 g (16.7 mmol) of triisopropylsilyl triflate. The reaction solution was stirred at room temperature for 3 h, diluted with ether, and then poured into a separatory funnel. The organic layer was washed three times with water. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate, concentrated *in vacuo*, and chromatographed through 225 g of silica gel that was slurry-packed with a 50% ether/hexane solution containing 1% triethylamine. Gradient elution from 50% ether/hexane to 2% methanol/ether afforded 1.746 g (76%) of the desired product **17**. The spectral data for a mixture of stereoisomers are as follows: ^1H NMR (300 MHz, $CDCl_3$) δ 4.68–4.62 (m, 1 H), 3.79 and 3.73 (2 s, total of

3 H), 3.68 and 3.67 (2 s, total of 3 H), 2.80–2.44 (m, 6 H), 2.38–2.32 (m, 1 H), 2.30–2.00 (m, 3 H), 1.86–1.76 (m, 1 H), 1.25–1.10 (m, 3 H), 1.09 (d, J = 6.1 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 172.1, 168.2, 129.1, 122,0, 58.1, 52.3, 51.5, 40.5, 32.5, 31.5, 27.2, 25.4, 24.7; IR (neat, NaCl) 2947, 2867, 1742, 1664, 1457, 1436, 1419, 1364, 1313, 1266, 1205 cm^{-1}; FAB-MS m/e (rel. intensity) 452 (MH^+ – 2 H, 100).

1-Aza-9-carbomethoxy-3-(2-carbomethoxyethyl)-2-oxo-5-(triisopropylsiloxy)bicyclo[4.3.0]non-3,5-diene (18) and 1-Aza-9-carbomethoxy-3-(2-carbomethoxyethyl)-2-hydroxy-5-(triisopropylsiloxy)bicyclo[4.3.0]-non-2,4,6,8-tetraene (19). To a solution of 1.531 g (3.38 mmol) of **17** in 34 mL of *p*-dioxane at room tempeature was added 0.843 g (3.72 mmol) of 2,3-dichloro-4,5-dicyanobenzoquinone. The resulting solution was refluxed for 3 h, cooled to room temperature, diluted with ether, and filtered to remove yellow solids. The filtrate was concentrated *in vacuo* and chromatographed through 175 g of silica gel that was slurry-packed with a 50% ether/hexane solution containing 1% triethylamine. Gradient elution from 50% ether/hexane to 5% methanol/ether afforded 0.769 g (51%) of the desired product **18**, 0.228 g (15%) of **19**, and 0.107 g (7%) of the recovered starting material **17**. The spectral data for **18** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1 H), 5.13 (dd, J = 9.4, 3.2 Hz, 1 H), 3.78 (s, 3 H), 3.64 (s, 3 H), 3.10 (dd, J = 9.2, 6.3 Hz, 2 H), 2.92–2.72 (m, 2 H), 2.67–2.62 (m, 2 H), 2.52–2.41 (m, 1 H), 2.33–2.23 (m, 1 H), 1.27–1.14 (m, 3 H), 1.09 (d, J = 6.4 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 173.8, 171.0, 159.1, 135.3, 134.7, 133.7, 129.0, 61.7, 52.5, 51.3, 32.3, 27.6, 26.4, 25.8, 17.6, 12.4; IR (neat, NaCl) 2948, 2926, 2867, 1742, 1668, 1587, 1559, 1436, 1369, 1317, 1205, 1179, 1121, 987, 883 cm^{-1}; GCMS (PCI) m/e (rel. intensity) 480 (M + 29, 14), 425 (M + 1, 100), 451 (M^+, 30), 420 ($M^+ - OCH_3$, 7), 88 (7), 87 (37), 75 (9), 74 (8), 61 (37), 55 (12); HRMS (EI) m/e calcd for $C_{23}H_{37}NO_6Si$ 451.2390, found 451.2389; TLC R_f = 0.37 using 2% methanol/ether; $[\alpha]^{21}_D$ –77.6° (CH_2Cl_2, c 1.0). The spectral data for **19** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 4.8 Hz, 1 H), 6.49 (d, J = 5.0 Hz, 1 H), 6.48 (s, 1 H), 3.88 (s, 3 H), 3.63 (s, 3 H), 2.87 (t, J = 7.5 Hz, 2 H), 2.60 (t, J = 7.5 Hz, 2 H), 1.37–1.22 (m, 3 H), 1.08 (d, J = 7.2 Hz, 18 H); IR (neat, NaCl) 2948, 2867, 1740, 1654, 1562, 1468, 1403, 1338, 1278, 1197, 1174, 1119, 1047, 1004, 917, 883, 839, 791 cm^{-1}; FAB-MS m/e (rel. intensity), 450 (M + 1, 100), 417 ($M^+ - CH_3OH$, 98), 342 (50); HRMS (EI) m/e calcd for $C_{23}H_{35}NO_5Si$ 449.2233, found 449.2218.

1-Aza-9-carbomethoxy-3-(2-carbomethoxyethyl)-5-hydroxy-2-oxobicyclo[4.3.0]non-3,5-diene (20). A solution of 0.253 g (0.560 mmol) of **18** in 70 mL of 0.01 N HCl in 1:1 methanol/water (v/v) was heated at 105 °C for 2 h in an oil bath. The solvent was removed *in vacuo*, and the residue was chromatographed through 100 g of silca gel that was slurry-packed with ether containing 1% triethylamine. Gradient elution from ether to 9% methanol/ether afforded 0.081 g (49%) of the desired product **20** and 0.0455 g (18%) of the recovered **18**. The spectral data are as follows: ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.27 (s, 1 H), 5.14 (dd, J = 9.5, 3.1 Hz, 1 H), 3.74 (s, 3 H), 3.63 (s, 3 H), 3.17–3.10 (m, 2 H), 2.90–2.71 (m, 2 H), 2.62 (t, J = 6.9 Hz, 2 H), 2.60–2.45 and 2.35–2.26 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 170.9, 159.0, 136.0, 134.3, 132.4, 128.5, 62.1, 52.6, 51.4, 32.4, 27.0, 26.5, 25.7; IR (neat, NaCl) 3500–3100, 2955, 2925, 2915, 1741, 1696, 1671, 1586, 1440, 1323, 1205 cm^{-1}; HRMS (EI) m/e calcd for $C_{14}H_{17}NO_6$ 295.1056, found 295.1052; TLC R_f = 0.27 using 5% methanol/ether; $[\alpha]^{21}_D$ –169.6° (CH_2Cl_2, c 1.5).

2-(Hydroxymethyl)-*N*-(2-(3-hydroxypropyl)-4-hexynoyl)piperidine. To a solution of 24.7 g (214 mmol) of *d,l*-2-piperidinemethanol in 350 mL of toluene at 0 °C was added dropwise 110 mL (220 mmol) of a 2.0 M solution of trimethylaluminum in toluene. After the solution was stirred at room temperature for 1 h, a solution of 27.2 g (179 mmol) of **5** in 250 mL of toluene was added dropwise. The resulting solution was refluxed for 1.5 h and cooled to 0 °C, and a 30% (w/w) sodium potassium tartrate solution was cautiously added. The mixture was stirred vigorously for 2.5 h and transferred to a separatory funnel to separate the organic layer. The aqueous layer was extracted with dichloromethane (5 × 100 mL). The combined organic layers were dried over sodium sulfate, concentrated *in vacuo*, and chromatographed through 400 g of silica gel that was slurry-packed with a 7% methanol/ether solution. Gradient elution from 7% methanol/ether to 10% methanol/ether afforded 47.3 g (99%) of the desired amide product. The spectral data for a mixture of stereoisomers are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89–4.77 (m, 0.5 H), 4.61 (br d, J = 12.6 Hz, 0.5 H), 4.32–4.20 (m, 0.5 H), 3.97–3.86 (m, 1 H), 3.86–3.70 (m, 2.5 H), 3.70–3.52 (m, 4 H), 3.21–3.08 (m, 1 H), 3.02–2.90 (m, 0.5 H), 2.66 (t with fine coupling, J = 13.2 Hz, 0.5 H), 2.46–2.20 (m, 2 H), 1.84–1.50 (m, 12 H); ^{13}C NMR (75 MHz, C_6D_6) δ 175.2, 174.9, 77.8, 77.5, 76.9, 76.6, 62.6, 62.4, 62.3, 60.4, 55.1, 55.0, 51.1, 50.7, 42.4, 42.0, 41.0, 40.8, 40.5, 37.4, 30.8, 30.6, 30.4, 29.6, 29.4, 29.1, 26.6, 26.4, 26.3, 25.9, 25.2, 24.9, 23.6, 23.2, 20.0, 19.5, 19.5, 3.6, 3.5, 3.4; IR (neat, NaCl) 3373 (br), 2936, 2866, 1610, 1447, 1364, 1258, 1058 cm^{-1}; FAB-MS m/e (rel. intensity) 268 (M + 1, 100), 250 (M^+ – OH, 10), 116 (52); HRMS (CI) m/e calcd for ($C_{15}H_{25}NO_3$ + H) 268.1913, found 268.1917; HRMS (EI) m/e calcd for ($C_{15}H_{25}NO_3 - OCH_3$) 236.1650, found 236.1647. Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.40; H, 9.67; N, 5.64. TLC R_f = 0.33 using 10% methanol/ether.

2-Carbomethoxy-*N*-(2-(2-carbomethoxyethyl)-4-hexynoyl)piperidine (25). To a solution of 23.7 g (88.8 mmol) of the diol in 800 mL of acetone at 0 °C was added dropwise 179 mL of Jones reagent. After the addition was completed, the reaction mixture was stirred at room temperature for 4 h. Methanol was added to quench any excess Jones reagent until a characteristic green color of the Cr^{3+} salts was obtained. The solids were decanted and filtered through a plug of glass wool. The acetone in the filtrate was removed *in vacuo*, and the residue was dissolved in water. The aqueous layer was saturated with ammonium chloride and then extracted with ethyl acetate (5 × 100 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo* to yield 20.4 g of the crude diacid. *N,N*-Dimethylformamide dimethyl acetal (66.0 g) was added dropwise to a solution of 20.4 g of this diacid in 130 mL of toluene at 80 °C. The reaction mixture was refluxed for 2 h and then cooled to room temperature. The solution was diluted with 500 mL of ether and washed with saturated aqueous sodium bicarbonate solution (3 × 100 mL), water (1 × 100 mL), and saturated aqueous sodium chloride solution (1 × 100 mL). The combined organic layers were dried over sodium sulfate, concentration *in vacuo*, and immediately chromatographed through 450 g of silica gel that was slurry-packed with a 60% ether/hexane solution. Gradient elution from 60% ether/hexanes to 80% ether/hexane afforded 13.2 g (46%) of the desired product **25** over the two steps. The spectral data for a mixture of stereoisomers are as follows: ^{1}H NMR (300 MHz, C_6D_6) δ 5.69 (d, J = 4.3 Hz, 0.37 H), 5.63 (d, J = 4.8 Hz, 0.31 H), 4.92 and 4.88 (2 br s, total of 0.16 H), 4.71 (d, J = 5.2 Hz, 0.16 H), 3.64 (br t, J = 12.9 Hz, 1 H), 3.38, 3.34, 3.32, 3.29, and 3.25 (5 s, total of 6 H), 3.16–2.92 (m, 2 H), 2.68–2.55 (m, 1 H), 2.46–2.16 (m, 5 H), 2.14–2.00 (m, 2 H), 1.59, 1.53, and 1.50 (3 t, J = 2.5 Hz, total of 3 H), 1.32–1.10 (m, 4 H); ^{13}C NMR (75 MHz, C_6D_6) δ 173.9, 173.5, 173.2, 171.7, 171.6, 171.4, 77.5, 77.3, 77.1, 77.0, 76.8, 56.5, 52.2, 56.8, 51.6, 51.5, 51.0, 43.6, 43.4, 39.9, 39.7, 31.4, 31.3, 30.9, 28.1, 27.8, 27.7, 27.4, 26.9, 26.4, 25.7, 25.1, 23.7, 22.8, 22.3, 21.3, 3.4; IR (neat, NaCl) 2951, 2860, 1735, 1645, 1437, 1369, 1319, 1262, 1208, 1161, 1016 cm^{-1}; GCMS (PCI) m/e (rel. intensity) 352 (M + 29, 7), 325 (M + 2, 8), 324 (M + 1, 30), 292 ($M^+ - OCH_3$, 16), 182 (10), 181 (51), 170 (7), 145 (17), 144 (100), 142 (36), 93 (8), 84 (32); HRMS (EI) m/e calcd for $C_{17}H_{25}NO_5$ 323.1733, found 323.1726; TLC R_f = 0.41 using 80% ether/hexane.

1-Aza-10-carbomethoxy-3-(2-carbomethoxyethyl)-2,5-dioxobicyclo-[4.4.0]decane (27a and 27b). To a cool, oven-dried 50-mL three-neck flask were added 3.370 g (10.4 mmol) of **25**, 20 mL of methanol, and 0.181 g of tetraethylammonium tosylate. The solution was degassed by sonication under a slow stream of nitrogen for 5 min. A carbon rod anode and a platinum wire cathode were inserted, and the solution was electrolyzed at a constant current of 35.4 mA. After 5.1 F of charge had been passed, the reaction mixture was poured into a round-bottom flask and concentrated *in vacuo*. The viscous liquid was immediately chromatographed through 200 g of silica gel that was slurry-packed with a 60% ether/hexane solution. Gradient elution from 60% ether/hexane to 80% ether/hexane afforded 3.30 g of a mixture of the α-methoxylated amide and the recovered **25**.

A 1.0 M titanium(IV) chloride in dichloromethane solution (23.4 mL, 23.4 mmol) was added dropwise to a solution of 3.30 g of the above mixture in 93 mL of dichloromethane at –78 °C. The reaction mixture was allowed to reach ambient temperature on its own and stirred at room temperature for 36 h. A 30% (w/w) aqueous sodium potassium tartrate solution (75 mL) was slowly added, and the mixture was stirred vigorously for 1 h. The phases were separated, and the aqueous layer was extracted with dichloromethane (10 × 60 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to yield a yellow viscous oil (*ca.* 3.50 g).

A solution of *ca.* 3.50 g of the viscous oil in 100 mL of methanol at –78 °C was ozonolyzed for 0.75 h after the first appearance of a blue color. Nitrogen was then bubbled though the solution for 15 min. Zinc dust (1.50 g) and 3.67 g of acetic acid were added. After being stirred at room temperature for 72 h, the reaction mixture was filtered by suction.

The filtrate was concentrated *in vacuo* and chromatographed though 225 g of silica gel that was slurry-packed with an 80% ether/hexane solution. Gradient elution from 80% ether/hexane to 4% methanol/ether afforded 0.968 g (30%) of minor isomer **27a** and 1.4234 g (44%) of major isomers **27b**. The spectral data for minor isomer **27a** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (dd, J = 6.0, 1.9 Hz, 1 H), 4.07 (dd, J = 11.8, 3.5 Hz, 1 H), 3.75 (s, 3 H), 3.68 (s, 3 H), 2.78–2.59 (m, 3 H), 2.50 (t, J = 7.4 Hz, 2 H), 2.29 (br d, J = 13.8 Hz, 1 H), 2.22–2.13 (m, 2 H), 1.92–1.80 (m, 2 H), 1.75–1.61 (m, 1 H), 1.42–1.33 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 173.6, 172.7, 171.7, 61.5, 52.3, 51.6, 40.2, 38.1, 31.0, 28.3, 25.9, 25.9, 20.2; IR (neat, NaCl) 2954, 2864, 1734, 1651, 1437, 1294, 1205, 1172, 1096, 1072 cm^{-1}; GCMS (PCI) m/e (rel. intensity) 340 (M + 29, 13), 313 (M + 2, 26), 312 (M + 1, 100), 311 (M^+, 14), 310 (31), 280 ($M^+ - OCH_3$, 65), 279 (12), 252 ($M^+ - COOCH_3$, 12), 224 ($M^+ - CH_2CH_2COOCH_3$, 7); HRMS (EI) m/e calcd for $C_{15}H_{21}NO_6$ 311.1369, found 311.1382. Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.76; H, 6.77; N, 4.45. The spectral data for major isomers **27b** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (d with fine coupling, J = 4.3 Hz, 0.5 H), 4.54 (t, J = 5.8 Hz, 0.5 H), 4.00–3.90 (m, 1 H), 3.75, 3.73, 3.69, and 3.68 (4 s, total of 6 H), 2.97–2.87 (m, 1 H), 2.81–2.70 (m, 0.5 H), 2.67–2.59 (m, 1 H), 2.57–2.46 (m, 2.5 H), 2.33 (br d, with fine coupling, J = 14.1 Hz, 0.5 H), 2.23–2.08 (m, 1.5 H), 2.04–1.96 (m, 1 H), 1.95–1.55 (m, 4 H), 1.42–1.37 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 205.6, 174.1, 173.9, 173.4, 172.7, 172.0, 171.4, 61.4, 60.7, 54.0, 52.4, 52.0, 51.6, 40.4, 39.7, 39.0, 37.4, 30.9, 30.8, 29.4, 28.9, 25.9, 25.7, 24.9, 24.8, 23.9, 20.5, 17.7; IR (neat, NaCl) 2954, 2864, 1734, 1653, 1436, 1301, 1210, 1174, 1077 cm^{-1}; GCMS (PCI) m/e (rel. intensity) 340 (M + 29, 12), 312 (100), 311 (16), 310 (39), 280 (79), 279 (22), 252 (21), 224 (15); HRMS (EI) m/e calcd for $C_{15}H_{21}NO_6$ 311.1369, found 311.1359.

1-Aza-5-(*tert*-butyldimethylsiloxy)-10-carbomethoxy -3-(2-carbomethoxyethyl)-2-oxobicyclo[4.4.0]dec-4-ene (29a) and 7-Aza-1-(*tert*-butyldimethylsiloxy)-6,11-dicarbomethoxy-8-oxotricyclo[7.2.1.0^{2,7}]dodecane (30a). To a solution of 0.219 g (0.704 mmol) of **27a** and 0.53 g of triethylamine in 1.4 mL of toluene at 0 °C was added 1.02 g of *tert*-butyldimethylsilyl triflate. The reaction was monitored by TLC for loss of starting material. When complete, 2 mL of methanol was added and the mixture was concentrated *in vacuo*. The crude was chromatographed through 85 g of silica gel that was slurry-packed with a 40% ether/hexane solution. Gradient elution from 40% ether/hexane to ether afforded 0.063 g (21%) of **29a** and 0.180 g (60%) of **30a**. The spectral data for **29a** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) (referenced to $CDCl_3$, 7.24 ppm) δ 5.62 and 5.56 (2 d with fine coupling, J = 5.9 Hz, total of 1 H), 4.66 (d, J = 3.6 Hz, 0.5 H), 4.63 (dd, J = 3.8, 1.3 Hz, 0.5 H), 3.86–3.74 (m, 1 H), 3.713, 3.706, 3.67, and 3.62 (4 s, total of 6 H), 3.16–3.06 (m, 1 H), 2.55–2.00 (m, 6 H), 1.97–1.83 (m, 1 H), 1.82–1.73 (m, 1 H), 1.66–1.50 (m, 1 H), 1.48–1.38 (m, 1 H), 0.89 (s, 9 H), 0.16 and 0.15 (2 s, total of 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 173.7, 171.3, 169.3, 168.8, 147.5, 147.3, 100.3, 100.2, 56.9, 56.6, 52.3, 51.7, 51.6, 39.2, 38.8, 31.1, 30.6, 30.4, 29.9, 29.8, 29.7, 29.4, 26.7, 26.1, 25.6, 21.2, 18.0, –4.6; IR (neat, NaCl) 2953, 2858, 1741, 1694, 1652, 1448, 1363, 1311, 1250, 1169, 1112, 1008, 880, 838, 782 cm^{-1}; GCMS (PCI) m/e (rel. intensity) 454 (M + 29, 16), 427 (31), 426 (M + 1, 100), 425 (M^+, 16), 394 ($M^+ - OCH_3$, 26), 368 (15), 73 (CH_2COOCH_3, 43). The spectral data for **30a** are as follows: ^{1}H NMR (300 Mhz, $CDCl_3$) (referenced to $CDCl_3$, 7.24 ppm) δ 5.15 (d, J = 4.7 Hz, 1 H), 3.69 (s, 3 H), 3.63 (s, 3 H), 3.45 (d with fine coupling, J = 11.5 Hz, 1 H), 3.10 (dd, J = 8.9, 6.0 Hz, 1 H), 2.81 (dd, J = 7.1, 4.6 Hz, 1 H), 2.38 (dd, J = 10.8, 4.6 Hz, 1 H), 2.35–2.27 (m, 1 H), 2.23 (d, J = 13.8 Hz, 1 H), 2.08 (d, J = 11.0 Hz, 1 H), 2.05–1.89 (m, 2 H), 1.85–1.76 (m, 1 H), 1.62–1.47 (m, 1 H), 1.38–1.12 (m, 2 H), 0.80 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 174.1, 171.7, 82.0, 64.1, 52.1, 51.7, 51.6, 45.2, 41.6, 36.9, 32.2, 26.0, 25.3, 24.3, 20.6, 17.7, –2.8, –3.0; IR (neat, NaCl) 2953, 2858, 1739, 1669, 1462, 1436, 1352, 1294, 1259, 1209, 1180, 1098, 1073, 875, 838, 776 cm^{-1}; GCMS (PCI) m/e (rel. intensity) 454 (M + 29, 22), 426 (M + 1, 100), 410 ($M^+ - CH_3$, 21), 394 ($M^+ - OCH_3$, 26), 368 (38); FAB-MS m/e (rel. intensity) 426 (M + 1, 100); HRMS (EI) m/e calcd for $C_{21}H_{35}NO_6Si$ 425.2234, found 425.2242.

1-Aza-10-carbomethoxy-3-(2-carbomethoxyethyl)-2,5-dioxo-4-(phenylselenenyl)bicyclo[4.4.0]decane (32a and 32b). Conversion of Compound 27a to 32a. To a solution of 0.90 mL of a 1.6 M *n*-butyllithium in hexane solution in 3 mL of tetrahydrofuran at –78 °C was added dropwise 0.203 g of 2,2,6,6-tetramethylpiperidine. After 15 min, a solution of 0.407 g (1.31 mmol) of **27a** in 3 mL of tetrahydrofuran was added. The reaction was maintained at –40 °C for 40 min, and the nitrogen line was replaced by a balloon filled with nitrogen. A solution of 0.37 g of benzeneselenenyl bromide in 1 mL of tetrahydrofuran was added at –78 °C, and the reaction was stirred at –40 °C for 45 min. The reaction was then quenched with saturated aqueous ammonium chloride solution and diluted with ether. The organic layer was washed twice with saturated aqueous ammonium chloride solution. The aqueous layer was extracted three times with ether. The combined organic layers were washed once with saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was chromatographed through 100 g of silica gel that was slurry-packed with a 50% ether/hexane solution. Gradient elution from 50% ether/hexane to ether afforded 0.293 g (48%) of the desired product **32a** and 0.041 g (14%) of the recovered **27a**. The spectral data for **32a** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.54 (m, 2 H), 7.38–7.28 (m, 3 H), 5.52 (d, J = 5.1 Hz, 0.4 H), 5.29 (d, J = 5.7 Hz, 0.6 H), 4.54 (dd, J = 11.6, 2.9 Hz, 0.4 H), 4.10 (dd, J = 12.2, 3.8 Hz, 0.6 H), 3.85 (d, J = 3.8 Hz, 0.6 H), 3.79 (d, J = 2.4 Hz, 0.4 H), 3.81, 3.73, 3.66, and 3.65 (4 s, total of 6 H), 3.04 (td, J = 8.0, 2.5 Hz, 0.6 H), 2.99–2.93 (m, 0.4 H), 2.56–2.24 (m, 4 H), 2.10–2.00 (m, 0.6 H), 1.87 (q, J = 7.5 Hz, 2 H), 1.80–1.25 (m, 3.4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 199.2, 173.1, 172.5, 171.3, 170.8, 170.6, 167.3, 134.9, 134.7, 129.4, 129.3, 128.8, 127.6, 127.2, 60.5, 59.0, 52.6, 52.3, 51.9, 51.6, 51.5, 49.8, 48.8, 46.2, 41.0, 31.3, 31.1, 29.0, 27.7, 26.1, 26.0, 23.5, 23.1, 20.9, 20.4; IR (neat, NaCl) 3056, 2952, 2863, 1735, 1654, 1458, 1370, 1300, 1206, 1170, 1072, 742 cm^{-1}; FAB-MS m/e (rel. intensity) 468 (M + 1, 90), 467 (12), 466 (50), 436 ($M^+ - OCH_3$, 78), 408 ($M^+ - COOCH_3$, 28), 378 (40), 312 (100), 224 (40), 164 (55); HRMS (EI) m/e calcd for $C_{21}H_{25}NO_6Se$ 467.0846, found 467.0801.

Conversion of Compound 27b to 32b. To a solution of 0.111 g of 2,2,6,6-tetramethylpiperidine in 2 mL of tetrahydrofuran at –78 °C was added dropwise 0.49 mL of a 1.6 M *n*-butyllithium in hexane solution. After 15 min, a solution of 0.222 g (0.712 mmol) of major isomer **27b** in 2 mL of tetrahydrofuran was added dropwise. The reaction mixture was stirred for 20 min at –78 °C and then at –40 °C for an additional 20 min. The reaction from this point onwards was performed under a balloon filled with nitrogen. The reaction was placed in a dry ice/acetone bath, and a solution of 0.21 g of benzeneselenenyl bromide was added. After the mixture was stirred at –40 °C for 40 min, the reaction was quenched with saturated aqueous ammonium chloride solution and diluted with ether. The organic layer was washed twice with saturated aqueous ammonium chloride solution. The aqueous layer was extracted twice with ether. The combined organic layers were washed once with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was immediately chromatographed through 200 g of silica gel that was slurry-packed with a 50% ether/hexane solution. Gradient elution from 50% ether/hexane to 70% ether/hexane afforded 0.150 g (45%) of the desired product **32b** and 0.030 g (14%) of the recovered starting material **27b**. The spectral data for **32b** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.52 (m, 2 H), 7.39–7.28 (m, 3 H), 5.41 (d with fine coupling, J = 5.8 Hz, 0.2 H), 5.36 (d with fine coupling, J = 5.8 Hz, 0.8 H), 4.32–4.29 (m, 0.2 H), 3.95 (dd, J = 12.1, 3.6 Hz, 0.8 H), 3.78 (2 overlapping d, 3 lines, J of 1 d = 2.2 Hz, J of the other d = 3.2 Hz, total of 1 H), 3.73 and 3.67 (2 s, total of 6 H), 3.14 (ddd, J = 10.0, 6.1, 2.2 Hz, 0.8 H), 2.90–2.80 (m, 0.2 H), 2.59–2.30 (m, 4 H), 2.25–1.70 (m, 5 H), 1.41–1.27 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 172.8, 171.0, 169.4, 135.4, 134.7, 129.5, 129.0, 129.0, 60.3, 52.4, 52.3, 51.7, 48.2, 45.7, 32.1, 30.8, 27.1, 25.9, 20.9; IR (neat, NaCl) 3056, 2952, 2862, 1735, 1657, 1571, 1438, 1376, 1329, 1300, 1209, 1171, 1097, 1073, 1047, 1022, 1000, 741 cm^{-1}; GCMS (PCI) m/e (rel. intensity) 468 (M + 1, 47), 328 (76), 324 (51), 310 (M^+ – SePh, 48), 296 (50), 159 (93), 158 (51), 157 (62), 89 (75), 73 (52), 61 (100), 59 (74); HRMS (CI) m/e calcd for ($C_{21}H_{25}NO_6Se$ + H) 468.0925, found 468.0893.

1-Aza-6-hydroxy-10-carbomethoxy-3-(2-carbomethoxyethyl)-2,5-dioxobicyclo[4.4.0]dec-3-ene (33). Conversion of Compound 32a to 33 Using MCPBA. To a solution of 0.0268 g (0.057 mmol) of **32a** in 1 mL of dichloromethane at 0 °C was added 0.040 g of *meta*-chloroperbenzoic acid (MCPBA). The reaction mixture was allowed to reach ambient temperature on its own. After 21 h, the reaction mixture was concentrated *in vacuo* and chromatographed through 13 g of silica gel that was slurry-packed with a 60% ether/hexane solution. Gradient elution from 60% ether/hexane to 90% ether/hexane afforded 0.0100 g (54%) of **33**.

Conversion of Compound 32b to 33 Using MCPBA. To a solution of 0.486 g (1.04 mmol) of **32b** in 10 mL of dichloromethane at room temperature was added 0.720 g of MCPBA. After 12 h, the reaction mixture was concentrated *in vacuo* and chromatographed through 130 g of silica gel that was slurry-packed with a 60% ether/hexane solution.

Gradient elution from 60% ether/hexane to 90% ether/hexane afforded 0.164 g (48%) of **33**. The spectral data are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (apparent s with fine coupling, 1 H), 5.60 (s, 1 H), 5.21–5.17 (m, 1 H), 3.83 (s, 3 H), 3.69 (s, 3 H), 2.85 (t, J = 7.2 Hz, 2 H), 2.63 (t, J = 7.2 Hz, 2 H), 2.35–2.25 (m, 2 H), 1.90–1.70 (m, 3 H), 1.62–1.50 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 175.3, 172.4, 163.1, 148.7, 129.7, 82.7, 77.2, 53.6, 53.4, 51.9, 31.9, 26.7, 25.8, 14.9; IR (neat, NaCl) 3393 (br), 2955, 2874, 2855, 1734, 1700, 1664, 1628, 1437, 1378, 1292, 1271, 1216, 1162, 1109, 1037, 989, 891 cm^{-1}; GCMS (PCI) m/e (rel. intensity) 309 (16), 308 ($MH^+ - H_2O$, 84), 307 (7), 278 (3), 277 ($MH^+ - H_2O - OCH_3$, 16), 276 (100), 275 ($MH^+ - H_2O - CH_3OH$, 100), 275 (10), 248 (6); HRMS (CI) m/e calcd for $C_{15}H_{18}NO_6$ ($MH^+ - H_2O$) 308.1134, found 308.1142.

1-Aza-10-carbomethoxy-3-(2-carbomethoxyethyl)-5-hydroxy-2-oxobicyclo[4.4.0]dec-3,5-diene (34). To a solution of 0.019 g (0.059 mmol) of **33** in 0.6 mL of chloroform were added 0.034 g of triethylsilane and 0.067 g of trifluoroacetic acid. The reaction was monitored by TLC. After 1.5 h, the reaction mixture was concentrated *in vacuo* (isopropyl alcohol used as the codistilling solvent) and chromatographed through 7.5 g of silica gel that was slurry packed with a 5% methanol/ether solution. Elution using 5% methanol/ether afforded 0.018 g (99%) of **34**. The spectral data are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.42 (br hump, 1 H), 7.26 (s, 1 H), 5.20 (dd, J = 6.3, 3.5 Hz, 1 H), 3.74 (s, 3 H), 3.62 (s, 3 H), *ca.* 2.96 (A part of an ABX_2 pattern, J = 18.1, 4.7 Hz, 1 H), 2.89–2.56 (m, 5 H), 2.38–2.27 (m, 1 H), 2.13–2.00 (m, 1 H), 1.88–1.76 (m, 1 H), 1.74–1.60 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 171.9, 160.3, 136.7, 132.0, 129.1, 126.3, 55.5, 52.6, 51.3, 32.4, 26.4, 25.6, 22.9, 15.8; IR (neat, NaCl) 3167 (br), 2954, 1740, 1653, 1583, 1541, 1438, 1415, 1357, 1283, 1205, 1050, 986 cm^{-1}; GCMS (PCI) m/e (rel. intensity) 310 (M + 1, 100), 309 (M^+, 27), 308 (45), 278 ($M^+ - OCH_3$, 26), 277 (7), 276 (35), 158 (21), 59 (7); HRMS (EI) m/e calcd for $C_{15}H_{19}NO_6$ 309.1212, found 309.1228.

1-Aza-5-hydroxy-10-carboxy-3-(2-carboxyethyl)-2-oxobicyclo[4.4.0]-dec-3,5-diene ((±)-A58365B). Conversion of Compound 34 to (±)-A58365B. To a mixture of 0.0168 g (0.054 mmol) of **34** and 0.004 g of tetrabutylammonium bromide at room temperature was added 0.3 mL of a 9 M hydrobromic acid in water solution. The reaction was heated at 110 °C for 45 min, cooled, and diluted with water. Dowex MR3 resin (0.060 g) was added, and the mixture was stirred for 30 min. This mixture was then filtered and concentrated *in vacuo*. The residue was purified by HPLC chromatography (Magnum-9 ODS-3, 50% acetonitrile/water to 40% acetonitrile/water in 120 min at 5 mL/min) to afford 0.013 g (85%) of (±)-A58365B as the desired product. The spectral data for (±)-A58365B are as follows: ^{1}H NMR (300 MHz, D_2O) (referenced to D_2O, 4.67 ppm) δ 7.25 (s, 1 H), 4.89 (dd, J = 6.3, 3.8 Hz, 1 H), *ca.* 2.72 (A part of an ABX_2 pattern, J = 17.9, 4.8 Hz, 1 H), 2.63–2.48 (m, 3 H), 2.43 (t, J = 6.8 Hz, 2 H), 2.18–2.06 (m, 1 H), 2.01–1.88 (m, 1 H), 1.70–1.58 (m, 1 H), 1.50–1.36 (m, 1 H); ^{13}C NMR (75 MHz, D_2O) δ 177.6, 175.2, 160.8, 136.7, 132.5, 131.7, 125.8, 56.5, 32.4, 25.5, 25.0, 22.7, 15.1; IR (neat, NaCl) 3600–2800 (br), 2948, 1718, 1653, 1522, 1419, 1281, 1255 cm^{-1}; UV λ_{max} (MeOH) (ϵ) 333 (4500), 233 (4100); FAB-MS m/e (rel. intensity) 282 (M + 1, 50); HRMS (FAB) m/e calcd for $C_{13}H_{16}NO_6$ 282.0978, found 282.0983.

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Supplementary Material Available: Proton and carbon NMR data for compounds **5**, **7**, **14**, **15–20**, **25**, **27a**, **27b**, **29a**, **30a**, and **32–34** and (±)-A58365B; proton, carbon, and fluorine NMR data for compound **12**; HMQC-TOCSY and HMBC data for **30a**; and HMQC–TOCSY data for **27a** (52 pages). Ordering information is given on any current masthead page.